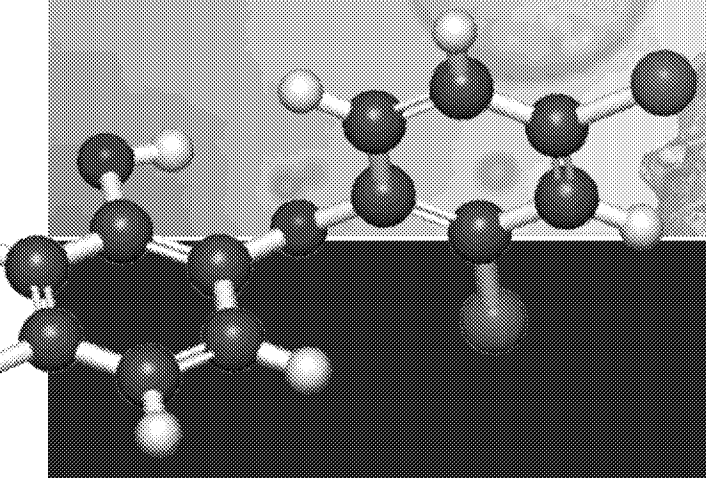
pptox IV

ENVIRONMENTAL STRESSORS IN DISEASE AND IMPLICATIONS FOR HUMAN HEALTH

OCTOBER 26 – 29, 2014

BOSTON, MA

SPEAKER ABSTRACT BOOK



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Environmental Stressors in Disease and Implications for Human Health

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Speaker Abstracts

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The androgenic action of stress during fetal development

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To date the concept of "endocrine disruption" has been limited to chemicals capable of interfering with the body's endocrine system and producing adverse developmental, reproductive, neurological, and immune effects. Endocrine disrupting chemicals (EDCs) in this class include pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers. We propose to expand the concept of endocrine disruption to include non-chemical exposures that may also interfere with the body's endocrine system and produce adverse health effects. Multiple stressors may alter endocrine function. Examples include psychosocial stress, hyperthermia and malnutrition. For example, in rodents prenatal stress disrupts the normal surge of testosterone in the developing male and appears to act as an androgen on the developing female. Here we present data from two multi-center pregnancy cohort studies in which we examined a measure of psychosocial stress in relation to two androgen sensitive, sexually dimorphic endpoints; anogenital distance (AGD) and play behavior at 4-7 years of age. Pregnant women were enrolled into The Study for Future Families (SFF) in four U.S. cities in 2000-2002. Participants were asked about the occurrence of major stressful life events during pregnancy and AGD was measured in their infants at mean age 16 months. After adjustment for age and body size, females born to couples reporting high stress had significantly longer (i.e. more masculine) AGD than females born to couples reporting low stress ($p = 0.015$). When these children were 4-7 their mothers were asked to complete the Preschool Activities Inventory (PSAI), a standardized questionnaire that measures sexually dimorphic play behavior. We found that girls, but not boys, with a history of more prenatal stressful life events had significantly more masculine scores than those with fewer life events ($\beta = 3.48$, $p = 0.006$). In The Infant Development and the Environment Study (TIDES) women were enrolled in four US cities in their first trimester in 2010-2012 and infant AGD measured in their infants at birth. Phthalate metabolite concentrations were measured in first trimester urine samples and women reported on major stressful life events during pregnancy. While we did not see a direct effect of stress on AGD in this second study, we saw strong evidence for an interaction of maternal stress and phthalate exposure on boy's AGD. For example, among boys ($N = 365$) increasing concentration of (molar) sum DEHP metabolites, a known anti-androgen, was associated with a shorter (less masculine) AGD. However, when stratifying by number of stressful life events, this association was only seen in those with low ($\beta = -2.84$, $p = 0.002$) but not high stress ($\beta = -0.48$. $p = 0.54$). Together these preliminary data suggest that prenatal stressful life events may exert androgenic action and alter sexually dimorphic development endpoints.

Source(s) of support: Grants from the National Institute of Environmental Health Sciences (R01ES016863-04 and R01-ES09916) The Office for Research on Women's Health (K12 ES019852-01) and the U.S.Environmental Protection Agency

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Keywords: Birth Cohort, Epidemiology, Endocrine disruption

Presented in Session: Plenary I: Developmental exposures and altered reproductive systems in men and women
Date/Times: Monday, October 27, 8:30-10:00 AM

Prenatal origin of polycystic ovarian syndrome

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Polycystic ovary syndrome (PCOS) is a common female endocrinopathy combining ovarian and metabolic components with long-term cardiovascular outcomes. The high prevalence of PCOS and its broad clinical sequelae have raised interest in the etiopathogenesis of the syndrome. Although the pathogenetic pathways leading to PCOS remain largely unknown, the syndrome appears to have early fetal origins.An abnormal or altered fetal environment may potentially contribute to the pathogenesis of PCOS. The maternal-intrauterine environment can alter epigenetic processes in the placenta and fetus that program developmental changes associated with PCOS. Animal models of PCOS have been established through investigation of the effects of androgen excess during pregnancy. Prenatal androgenization of a female fetus results in the development of PCOS-like features in non-human primates, including polyfollicular ovaries, increased luteinizing hormone, distortion of neuroendocrine feedback and disordered estrous cycles in adult offspring. Ddirect fetal exposure to androgens was shown to impair ovarian expression of steroidogenic genes. Metabolic aberrations such as insulin resistance, fatty liver, impaired b-cell function and perturbed insulin signaling in metabolic tissues have been reported in animal experiments of prenatal androgenization as well.Although evidence derived from animal studies has been large and convincing, data for prenatal androgen excess in human gestations remain scarce and inconclusive.Fetal exposure to environmental substances known as endocrine disruptors (EDs) may affect the adult ovary, leading to polycystic changes. The main ED linked to PCOS-like programming effects is Bisphenol A (BPA) and its effects have been observed in mammals including mouse, rat, sheep, and monkey as well as human fetal ovaries exposed in vitro. Available studies suggest that exposure during ovary development can adversely affect several different aspects of early oogenesis as well as impair ovarian steroidogenesis. In the same context, perinatal exposure to BPA may program an altered metabolic phenotype in adult life, including obesity, hyperinsulinemia and glucose intolerance. These effects have been observed with low doses of BPA and normal diet, while high-fat diet may further exacerbate metabolic aberrations potentially leading to full-blown metabolic syndrome. Overall, the theory for fetal origins of PCOS is still open to investigation. Future studies should explore the presence, the source, the timing and the effects of fetal androgen excess as a potential etiological factor for PCOS in the female offspring.

Source(s) of support:

Reference(s):

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Abstract type: Translational Research
Category: Reproductive System
Keywords: Exposure Assessment, Prenatal, Postnatal

Presented in Session: Plenary I: Developmental exposures and altered reproductive systems in men and women
Date/Times: Monday, October 27, 8:30-10:00 AM

Organochlorine pesticide exposure and development in boys through puberty

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Although studies in experimental animals have shown that organochlorine pesticides (OCP) alter pubertal development, there are few epidemiological studies. We therefore evaluated the associations of serum OCP concentrations [hexachlorobenzene (HCB), β-hexachlorocylohexane (β-HCH), and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE)] with age of pubertal onset and sexual maturity among a cohort of Russian boys from Chapaevsk, a town historically environmentally contaminated with OCPs. From 2003-2005, 499 8-9 year-old boys were enrolled and followed annually for eight years. For this analysis, in a subset of 350 boys who had measured OCPs, we used multivariable interval censored models to evaluate associations of OCPs (quartiles) with three physician-assessed measures of pubertal development: Tanner stage for genitalia (G1-5), pubic hair (P1-5), and testicular volume (TV). In adjusted models, boys with higher HCB concentrations had later mean ages of pubertal onset based on TV > 3 mL and P2+ (but not G2+). Mean age at attaining TV > 3 mL was delayed 3.6, 7.9, and 4.7 months for HCB Q2, Q3, and Q4, respectively, compared to Q1 (trend p: 0.06). Boys with higher HCB concentrations reached P2+ 0.1 months earlier for Q2, 4.7 months later for Q3 and 4.6 months later for Q4 compared to Q1 (trend p: 0.04). There were no associations of serum β-HCH and p,p'-DDE concentrations with age of pubertal onset. In adjusted models of sexual maturity, boys with higher HCB concentrations achieved TV ≥ 20 mL a mean of 3.1 months, 5.3 months, and 5.0 months later for quartiles Q2, Q3, and Q4, respectively compared to Q1 (trend p=0.04). G5 was attained a mean of 2.2 months, 5.7 months, and 3.7 months later for β-HCH concentrations in Q2, Q3, and Q4 respectively as compared to Q1 (trend p=0.09). Finally, P5 occurred 6-9 months later on average for boys in the highest vs. lowest quartile for HCB (trend p=<0.001), β-HCH (trend p=0.01), and p,p'-DDE (trend p=0.04). No associations were observed between p,p'-DDE and G5 or TV ≥ 20 mL. In conclusion, higher prepubertal serum HCB concentrations were associated with later age of pubertal onset (defined as TV > 3 and P2+) and later maturity (TV ≥ 20 mL and P5). The results for HCB reflect a mean delay in both pubertal onset and attainment of sexual maturation, suggesting that on average, the tempo of puberty did not change. Higher serum p,p'-DDE levels were associated with later pubic hair maturation, but not genital or testicular maturation. β-HCH was associated with a later age of sexual maturity based on G5 and P5. Our findings add new evidence to the limited literature and suggest that prepubertal exposure to environmental OCPs at relatively high levels, especially HCB, may affect age of pubertal onset and sexual maturity in boys. Additional research is needed to understand the implications of environmentally-induced shifts in age at pubertal onset and sexual maturity on reproductive as well as psychosocial health.

Source(s) of support: This work was funded by the U.S. Environmental Protection Agency (grant R82943701), the National Institute of Environmental Health Sciences (grant R01 ES014370, P30 ES000002, and R03 ES017117). TL was supported by the National Institute for Occupational Safety and Health training grant T42-OH008416-09.

Reference(s):

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Keywords: Epidemiology, Postnatal, Puberty

Presented in Session: Plenary I: Developmental exposures and altered reproductive systems in men and women
Date/Times: Monday, October 27, 8:30-10:00 AM

Sperm abnormalities in young men with lifetime exposure to dichlorodiphenyldichloro-ethylene (p,p'-DDE) and polychlorinated biphenyls (PCBs)

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Due to their relative frequency and serious consequences that include congenital abnormalities and transgenerational effects,the potential impacts of environmental chemicals on sperm abnormalities need investigation.This study evaluated the effect of lifetime environmental exposure to organochlorines, including p,p´DDE and PCBs(118,138,153,&180)on sperm sex chromosome aneuploidy in young men from the general population of the Faroe Islands.Ninety men randomly sampled from the Faroe Islands Cohort study,an ongoing study investigating the impacts of exposures to environmental contaminants on health and development, were studied.Exposures were measured in cord blood and in samples taken at age 14 and in adulthood,at which time semen samples were also collected.p,p'-DDE, and PCBs(118,138,153,&180) were measured using a two-stage solid-phase extraction method,followed by gas chromatography analysis with electron capture detection, adjusted for total serum lipid content.Semen samples were categorized according to WHO 2010guidelines,and analyzed using sperm fluorescence in-situ hybridization(FISH).Σ4PCB was calculated by summing the four PCB congeners. Poisson regression was used to evaluate separate associations between p,p'-DDE, PCBs,and each of the disomy measures while adjusting for age,abstinence time, smoking,log sperm concentration,motility,&morphology.The mean age of the sample was 25 years and the mean BMI was 25.3kg/m2. Twelve percent had sperm concentrations<15million/mL, 2%had<40% total motile sperm,& 26%had<4% normally shaped sperm. Comparing the highest to the lowest tertile,p,p'-DDE was associated with significant increased risk of XX18(IRR=1.99;95%CI:1.65,2.45),XY18(IRR=1.87; 95% CI:1.76,2.10),&total disomy(IRR=1.49;95%CI:1.37,1.63).Similarly,Σ4PCBs was associated with significant increased risk of XX18(IRR=1.88;95%CI:1.50,2.37), XY18(IRR=1.48;95%CI:1.29,1.68),& total disomy(IRR=1.30;95%CI:1.18,1.43).There were decreased risks between YY18, & increasing levels of p,p'-DDE and Σ4PCBs. In evaluating exposures measured prenatally within a subset(n=40),prenatal Σ4PCBs exposure showed a significantly increased trend in the risk of XY18(IRR=1.16;95% CI:1.03,1.30).Other significant associations between p,p'-DDE and Σ4PCBs at age 14 and adult sperm disomy were also observed. Results demonstrated an increase in the rate of XX18 and XY18, and total sex-chromosome disomy by increasing levels of p,p'-DDE and Σ4PCBs exposures, after adjustment for potential confounders. Evidence of this association was also seen prospectively–prenatal and age 14 organochlorine levels were associated with subsequent sperm disomy in adulthood. The Faroes Cohort has been a valuable context for investigating in utero exposures and subsequent indices of reproductive health. To our knowledge, this is the first study to evaluate the association between prenatal exposure to organochlorines and sperm aneuploidy,& how in utero chemicals impact testis health needs deeper study.

Source(s) of support:

Reference(s):

Abstract type: Translational Research
Category: Reproductive System
Keywords: Exposure Assessment, Other: Aneuploidy

Presented in Session: Plenary I: Developmental exposures and altered reproductive systems in men and women
Date/Times: Monday, October 27, 8:30-10:00 AM

Environmental estrogens activate non-genomic signaling to developmentally reprogram the epigenome

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Category: Other: Epigenome
Keywords:

Presented in Session: Breakout 1: Advances and insights from epigenetics
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Validation of altered epigenetic marks in human blood cells

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About 45 million (~19%) U.S. adults smoke, 46 million are former smokers and >100 million are exposed to environmental tobacco smoke. The mechanisms linking tobacco smoke to adverse health outcomes are largely unknown and exposure-altered epigenetic factors may play a role. Using epigenome-wide association, Joubert et al (Env Health Perspectives, 2012) observed highly significant associations ($p<10^{-7}$) between maternal smoking and DNA methylation in cord blood at 26 CpG sites in 10 genes. These changes appear to be associated with in utero tobacco smoke exposure.

We tested if four previously identified, smoking-associated CpGs located in 4 genes, were biomarkers of tobacco exposure in adults. Methylation was measured in whole blood DNA from adult smokers (5-70 cigarettes/day, n=179) and nonsmokers (n=79) using Illumina 450K arrays. We examined current smoking, pack-years, and methylation level adjusting for age. In newly recruited subjects (n=21), purified CD15+ granulocytes, CD14+ monocytes, CD19+ B cells, and CD2+ T cells were assessed with 450K arrays, Reduced Representation Bisulfite Sequencing and Methylation-specific PCR melt (MS-PCR) profiles. Three of four tested candidate CpGs (in AHRR, GFI1 and MYO1G) were strongly associated with ever smoking ($p<10^{-21}$), current smoking and pack-years of smoking. In addition, at least 6 other CpGs located in each gene achieved genome-wide significance. The CYP1A1 gene, which was strongly associated with tobacco smoke exposure in cord blood, showed no association with smoking in adults. Several CpG sites in the ALPPL2 gene were strongly associated with smoking ($p<10^{-24}$) and several previously identified CpGs were confirmed. As reported in other studies, cg05575921 was the most dramatically affected CpG ($p<10^{-70}$) by smoking and we confirmed the methylation change using MS-PCR melt profiles. Replication and validation of smoking-associated changes in DNA methylation in AHRR have been remarkably consistent across published studies.

Comparing the AHRR cg05575921 across purified hematopoietic cell types (n=21), we observed significant ($p< 0.005$) smoking effects in each of CD15+ granulocytes, CD14+ monocytes, CD19+ B cells, and CD2+ T cells, however myeloid lineage cells displayed a greater magnitude change. In purified CD14+ monocytes the methylation level of the AHRR regulatory region containing cg05575921 was dramatically reduced in smokers and this change was verified using the RRBS technique. RRBS determined that the region adjacent to cg05575921 contains 6 additional CpGs that display similar changes. Based on ENCODE data, this region appears to be a poised enhancer. AHRR mRNA expression (RT-PCR, RNA-seq) was strongly induced, but fold-change varied considerably among smokers (1.6-25-fold). DNA methylation changes in AHRR were observed in all purified cell types, in whole blood and in isolated mononuclear cells confirming AHRR cg05575921 as a general hematopoietic biomarker of smoking.

Source(s) of support: Funded in part by the Intramural Research Program of the National Institute of Environmental Health Sciences and a grant from the NIH/FDA Center for Tobacco Research.

Reference(s):

Joubert, B.R. et. al. 450K Epigenome-Wide Scan Identifies Differential DNA Methylation in Newborn Related to Maternal Smoking During Pregnancy. Environmental Health Perspectives (2012).
Joubert, B.R., et. al. Maternal Smoking and DNA Methylation in newborns: In utero effect or epigenetic inheritance? Cancer Epidemiology, Biomarkers, & Prevention (2014).

Abstract type: Population Research
Category: Other: Hematopoietic
Keywords: Epigenetics, Mechanisms & Pathways, Tobacco smoke

Presented in Session: Breakout 1: Advances and insights from epigenetics
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Cell distribution prediction from DNA methylation data using a reference set derived from umbilical cord blood

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Changes in cord blood DNA methylation may underlie observed associations between prenatal exposures and health outcomes. Many groups use the Infinium450K array to measure DNA methylation in stored total white blood cell (TWBC) DNA from birth cohort cord blood. Because DNA methylation is tissue-specific, failure to account for cell distribution can confound hypothesized exposure-to-methylation associations, leading to spurious results or failure to detect true relationships. Houseman et al. have developed a method using regression calibration to adjust for cellular mixture requiring reference methylation data; 2 datasets are now available, both derived from adult blood. Cells represented in these datasets may not reflect the most prevalent cellular components of cord blood, leading some to question whether they are optimal when applied to cord blood.

We used flow cytometry to separate cord blood into its most prevalent components and the 450K array to generate a reference set. Our objectives were to compare our cord-derived reference set to existing datasets for predicting cell distribution in cord TWBC; and conduct a proof-of-principal analysis to determine if maternal age at delivery predicts cord CpG methylation in a NYC-based cohort and if this association is confounded by cell-type distribution using each of the 3 reference sets.

We calculated the root mean squared error (RMSE) using each of the reference datasets to predict the true distribution of cord blood cells counted using flow cytometry. We found that the average RMSE was ~2% using our cord-derived reference set, compared to ~22% and ~30% for the Renius and Houseman reference datasets, respectively.

We used regression analyses to determine if maternal age was associated with methylation, both before and after accounting for predicted cell distribution using all 3 methods. Before correcting for cell-type, maternal age was associated with methylation at 134 CpG sites after correcting for multiple testing. After adjusting for cell type, we found that the # of significant sites was reduced to 25 using our cord reference set, 10 and 22 using other 2 reference sets. Only 1/3 of the Renius and Houseman significant sites overlapped with the 25 sites in our dataset, with 2 sites significant across all 3 analyses.

We found that the cord-derived reference set is better at predicting true cell distribution in cord blood than the adult-derived reference sets. The association between maternal age and methylation in cord blood was confounded by cell-type and after accounting for this, the # of significant sites was reduced, indicating that false positives may have been effectively removed. However, the adult-derived reference sets may over-adjust for cell-type in cord blood, as many of the cells represented in the adult-derived reference sets are present only in low proportion in cord blood. Additional analyses involving simulation to further evaluate this hypothesis are underway.

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Presented in Session: Breakout 1: Advances and insights from epigenetics
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Are differences in methylation in cord blood DNA associated with prenatal exposure to alcohol?

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Fetal alcohol spectrum disorders (FASD) are known to cause neurological and developmental abnormalities linked to prenatal alcohol exposure. The mechanisms involved are largely unknown, but they could include developmental programming effects, such as epigenetic changes caused by ethanol crossing the placenta. In particular, preliminary evidence exists from animal models that some genes are hyper- or hypo-methylated, but replication in human studies is currently lacking. The aim of this work was to investigate cord-blood DNA methylation profiles of offspring differentially exposed to alcohol in utero, using both a genome-wide and a candidate gene approach (with candidates in pathways likely to be targeted/disrupted by early ethanol exposure).

This study was based on the Avon Longitudinal Study of Parents and Children (ALSPAC). Genome-wide methylation analyses were carried out using the Illumina Infinium 450k chip (n~1000 offspring), and candidate gene analyses employed a 96-probe custom Illumina GoldenGate array designed to interrogate up to 24 genes (~4 CpG sites per gene) (n~500 offspring). A rigorous quality control pipeline was implemented for the Illumina Infinium data. Adjustments for maternal age, education, smoking in pregnancy and ethnicity were included in all alcohol exposure-methylation regressions to control for confounding. To further limit confounding by other lifestyle characteristics, we also used a Mendelian Randomization approach and compared offspring grouped according to maternal genotype (a functional SNP in the alcohol-metabolising gene ADH1B), instead of grouping them according to maternal reported alcohol use. This latter approach however was limited to the analysis of candidate gene methylation due to sample size limitations.

The two approaches are complementary to each other in a number of ways, and overlapping samples and CpGs tested ensure that validation and replication can both be carried out using these data. Further strengths of this project are the focus on causal effects (aided by using Mendelian Randomization) and more generally on the specificity of alcohol-dependent signals. Preliminary results from both approaches will be presented at the conference, as well as more details on the study design and criteria for selection of candidate genes and CpG sites to target within those genes.

Source(s) of support:
Reference(s):

Abstract type: Population Research
Category: Other: Epigenetic effects of intrauterine exposures
Keywords: Birth Cohort, Epigenetics, Prenatal

Presented in Session: Breakout 1: Advances and insights from epigenetics
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Placental epigenetic mechanisms

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Epidemiologic evidence has demonstrated that the intrauterine environment plays a central role in not only reproductive outcomes but also in defining the trajectory of health for the life of an individual. The molecular basis through which the fetus becomes programmed is complicated and likely involves epigenetic mechanisms such as DNA methylation, which are environmentally labile and allow for stable control of gene expression through development and beyond. Due to the tissue specificity and functional relevance of epigenetic mechanisms, the tissue chosen for examination is critical and results must be interpreted in light of that tissue's own physiologic function. The placenta is a key organ that controls the intrauterine environment, is responsible for appropriate development and for fetal programming, and can experience alterations at the molecular level from environmental exposures. We have begun to explore how the maternal environment, defined broadly, can impact the DNA methylation profiles of the placenta and in turn how these alterations are associated with developmental outcomes in children, including growth and neurobehavioral development. Using samples and data from our ongoing birth cohort in Providence, Rhode Island, we have examined specific genes as well as profiled the genome-wide DNA methylation status of greater than 450,000 CpG loci in nearly 200 placenta samples using the Illumina Infinium 450K methylation array. We have identified altered methylation of a number of loci in specific genes associated with in utero exposures to maternal obesity and gestational diabetes as well as to toxic metals and even socioeconomic stressors. We are now linking alterations to methylation of these genes with decrements in birth weight and in neurodevelopmental profile defined using the NICU Network Neurobehavioral Scales in the newborns. These results suggest a novel mechanism of action of the environment, operating through functional epigenetic alterations in the placenta which can potentially affect growth and neurodevelopment in children.

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Reference(s):

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Category: Nervous System
Keywords: Birth Cohort, Epigenetics, Prenatal

Presented in Session: Breakout 2: Role of the placenta in developmental origins of health and disease
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Sex-specific placental responses in fetal development

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Sexual differentiation is considered to begin at the formation of the male or female gonads. However, it is increasingly becoming apparent that the sexes respond differently to pre-natal environmental changes, including nutritional/metabolic, environmental chemicals, or stress, and these changes may be apparent as early as the zygotic stage of development. Differences in gene expression from autosomal and sex chromosomes may drive these differential responses. These embryonic changes are likely associated with later developmental origin of health and disease (DOHaD) effects. In general, females seem to be more resilient and better equipped to handle less than optimal in utero environments; whereas, males exposed to similar conditions eventually succumb to a variety of diseases, such as obesity, insulin resistance, other metabolic disorders, cardiovascular disturbances, and neurological disorders to list a few examples.

Given these sex differences in response in utero environmental conditions shifts, it is essential to understand when these differential responses may occur and their molecular origins. To address this concern, we have examined how murine embryos and conceptuses respond to altered nutrient conditions, including elevated in vitro glucose concentrations resembling concentrations present in the serum of diabetic mothers and maternal high fat diet leading to diet-induced obesity for conceptuses. As early as the blastocyst stage, it is possible to distinguish those cells that are destined to become the inner cell mass versus the trophectoderm cells, the progenitor placental cells. We have shown that murine zygotes cultured under the presence of elevated glucose concentrations (0.2mM D-glucose) exhibit reduced total and trophectoderm cell numbers at the blastocyst stage, but these adverse effects are not sex-dependent (1). Even so, nutritional disruptions may lead to gene expression differences between the sexes. Therefore, we next sought to determine whether altered nutrient conditions, in this case a high fat diet, led to sexually dimorphic differences in placental gene expression patterns. The placenta was chosen based on it being the central organ for fetal-maternal communication and nutrient acquisition by the fetus. In so doing, the placenta likely helps to maintain fetal homeostatis and may buffer the fetus against in utero environmental changes; whereas, failure of the placenta to respond rapidly to environmental fluctuations may be an initiating factor in later DOHaD effects. Our findings indicate that the placenta of female mice mounts a more robust gene expression response to a maternal high fat diet that is likely adaptive and shields this sex against later DOHaD effects (2). Further work is needed to determine if other in utero environmental challenges, including environmental chemicals and stress, result in similar sex differences in placental responses and how these early responses govern the risk for later disease risk.

Source(s) of support: NIH HD 44042

Reference(s):

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Abstract type: Basic Research
Category: Reproductive System
Keywords: Mechanisms & Pathways, Prenatal, Nutrition

Presented in Session: Breakout 2: Role of the placenta in developmental origins of health and disease
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

First trimester phthalate and phenol exposure is associated with miRNA alterations in the placenta

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Background: There is increasing concern that early-life exposure to endocrine disrupting chemicals (EDCs) can influence the risk of disease development. Phthalates and phenols are two classes of suspected EDCs that are used in a variety of everyday consumer products, including plastics, epoxy resins, and cosmetics. In utero exposure to EDCs may impact disease propensity through epigenetic mechanisms.

Objective: The objective of this study was to determine if prenatal exposure to multiple EDCs alters miRNA expression of human placenta, and if miRNA alterations were associated with birth outcomes.

Methods: Our study was restricted to a total of 179 women co-enrolled in the Harvard Epigenetic Birth Cohort and the Predictors of Preeclampsia Study. We analyzed correlations between first trimester urine concentrations of 8 phenols and 11 phthalate metabolites and expression of 29 candidate miRNAs in placenta by qRT-PCR.

Results: We found several statistically significant associations between miRNA expression and individual phenol and phthalate concentrations, as well as informative additive ($\sum$) biomarker groups of these metabolites. There were several significant associations between miRNA expression and additive $\sum$phenol groups, with fewer correlations among additive phthalates. For three miRNAs, miR-17-5p, miR-128, and miR-185, we detected a significant additive interaction between $\sum$phthalates and $\sum$phenols on expression levels. Using Gene Set Enrichment Analysis, we determined potential mRNA targets of these microRNAs were associated with several biological pathways, including the MAPKKK cascade.

Conclusions: Overall, these results suggest that prenatal phenol and phthalate exposure is associated with altered miRNA expression in placenta, suggesting a potential mechanism of EDC toxicity in humans.

Source(s) of support: Funding: This project was supported in part by a Pilot Project grant from the Harvard-NIEHS Center for Environmental Health (P30ES000002). Dr. LaRocca was supported by the Harvard University Center for the Environment Fellowship. A.M. Binder was supported by Training Grant T32HD060454 in Reproductive, Perinatal and Pediatric Epidemiology from the National Institute of Child Health and Human Development, National Institutes of Health. Dr. Michels was supported by grant K01ES015771 from the National Institute of Environmental Health Sciences, National Institutes of Health. The Epigenetic Birth Cohort was funded by research grant R21CA128382 from the National Cancer Institute, National Institutes of Health.

Reference(s):

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Category: Other: Epigenetics
Keywords: Birth Cohort, Epigenetics, Prenatal

Presented in Session: Breakout 2: Role of the placenta in developmental origins of health and disease
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Sexually dimorphic effect of gestational exposure to BPA on DNA methylation pattern in the rat placenta

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Changes in placental physiology following exposure to environmental factors such as endocrine disruptors, trigger an adaptive response. This supports the involvement of placenta in programming, and as such, its possible significance for subsequent adult health, otherwise termed developmental origin of health and disease (DOHaD). It has been reported that the sex of embryos may have an impact on how the placenta will respond to environmental "stressors".

Epigenetic mechanisms can affect gene expression and thereby predispose to some diseases even after cessation of exposure to an environmental factor. We hypothesized that alteration of DNA methylation in the placenta could provide early markers of exposure to endocrine disruptors. We aimed at studying the effect of a gestational exposure to Bisphenol A, a largely widespread endocrine disruptor, on DNA methylation pattern in female and male rat placenta.

Pregnant rats were exposed orally to BPA (10mg/kg/d) from gestational day 6 (GD 6) to 18. Placentas obtained by cesarean section were harvested at GD 19. Male and female placentas were identified using classical PCR for SRY expression. Genome-wide DNA Microarray analysis was performed to identify genes with aberrant methylation following gestational exposure. Additionally, possible changes in expression of DNA methylstranferases (DNMT1 and DNMT3a), enzymes that catalyze DNA methylation, were examined by RT-PCR in male and female placenta.

In female placenta, we identified a small number of genes that exhibited hypermethylation after BPA exposure with statistical significance (adjusted p-value < 0.05): SF-1 (log Fold Change : 1,21) ; Hmx2 (log FC : 1,36) ; Tctn2 (log FC : 1,45) and Mamdc4 (log FC : 1,14). In male placenta, one gene was significantly hypermethylated: Tnks2 (log FC : 1,92).

For DNMT3a expression, BPA exposure led to a sex-specific response since DNMT3a mRNA levels were significantly increased in male but not in female placenta. There was no effect of BPA on DNMT1 mRNA levels neither in male and female placenta.
In conclusion, prenatal exposure to a high dose of BPA lead to changes in DNA methylation pattern of various CpG islands in a sexually dimorphic manner, highlighting sex specific effects of early endocrine disruptor exposure on placental function that could be consistent with increased risk of disease later in life.

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Reference(s):

Abstract type: Basic Research
Category: Reproductive System
Keywords: Epigenetics, Experimental Models, Prenatal

Presented in Session: Breakout 2: Role of the placenta in developmental origins of health and disease
Date/Times: Monday, October 27, 10:30 AM - 12:00 PM

Paternal dietary effects on offspring metabolism

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An increasing number of studies in rodents and in humans link ancestral nutritional status with offspring metabolism. In our system, we find that male mice raised on low protein diet sire offspring with altered cholesterol metabolism, relative to control males. Other metabolic phenotypes reported in related systems include altered glucose tolerance, as well as cardiovascular changes such as altered blood pressure. I will present our latest studies focusing on the mechanistic basis for paternal dietary effects. Using in vitro fertilization, we have recently shown that sperm are at least partly responsible for this paternal effect. I will present out ongoing epigenomic studies in sperm, focusing on cytosine methylation and on RNAs in sperm.

Source(s) of support:

Reference(s):

Abstract type: Basic Research
Category: Reproductive System
Keywords: Epigenetics, Mechanisms & Pathways, Transgenerational

Presented in Session: Plenary II: Trans-generational inheritance
Date/Times: Monday, October 27, 1:30-3:00 PM

Genomic imprinting, physiology, and transgenerational inheritance

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Humans are widely exposed to endocrine disrupting chemicals (EDCs), including bisphenol A (BPA), and exposure is linked to developmental abnormalities in model organisms. The molecular mechanisms, however, are unclear and elucidating these pathways will provide insight into the windows of vulnerability and preventive measures. BPA has been linked to altered DNA methylation, indicating that epigenetic mechanisms may be relevant. We have recently reported effects of BPA exposure on genomic imprinting in the mouse. Imprinted genes are regulated by differential DNA methylation and aberrant imprinting disrupts fetal, placental, and postnatal development. We have demonstrated that in utero exposure to physiologically relevant doses of BPA disrupted expression of a number of imprinted genes, including the Snrpn, Ube3a, Igf2, Kcnq1ot1, Cdkn1c and Mash2 genes. Furthermore, the effects were tissue-specific with most genes affected in the placenta and fewer in the whole embryo. More importantly, DNA methylation analyses revealed that gene transcription changes were associated with altered methylation at differentially methylated regions.

Because our published data showed abnormal placentation in BPA-exposed mice and abnormal expression of genes relevant to growth (e.g., Igf2, Snrpn, and Cdkn1c), we subsequently determined whether early developmental exposure to BPA was associated with placental function alteration and postnatal growth impairment that may be associated with metabolic perturbation later in life. BPA-exposed male placentas were significantly smaller than controls at embryonic day 18.5; interestingly, no placental weight difference was observed in the females. Real time quantitative PCR assays revealed that placentas from BPA-exposed groups had significant alteration of mRNA expression of genes involved in glucose and amino acid transports, cortisol regulation, and vascularization, as compared to controls. During postnatal development, F1 BPA-exposed male mice had reduced body weight at birth but became heavier than controls as adults. Our physiological assays in F1 and F2 offspring have demonstrated that BPA exposure altered body fat content, glucose metabolism and pancreatic function in the male offspring. Specifically, these mice had higher body weight and/or fat, elevated liver triglyceride, impaired glucose tolerance and increased insulin resistance as compared to controls. These data suggested the potential ability of EDCs in altering the developmental programming of the offspring leading to increased risks of metabolic syndromes. Our ongoing studies are aimed to elucidate the relevant epigenetic and molecular mechanisms by investigating both the offspring and the pregnant mothers, as well as to continue investigating the potential transgenerational effects in the F3 and F4 generations.

Source(s) of support:

Reference(s):

Abstract type: Basic Research
Category: Other: Epigenetics
Keywords: Epigenetics, Prenatal, Transgenerational

Presented in Session: Plenary II: Trans-generational inheritance
Date/Times: Monday, October 27, 1:30-3:00 PM

Transgenerational effects on behavior resulting from BPA exposure

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Endocrine disrupting compounds (EDCs) act on steroid receptors, enzymes in the steroidogenic pathways, and/or via epigenetic modifications. These compounds can influence development of many organs, including the brain. Our laboratory has examined the effects of one of these EDC's, Bisphenol A (BPA), on juvenile and adult behaviors in laboratory mice. We have developed a paradigm for raising F1 to F4 mice that includes these key features: 1) exposure to a human-relevant dose of BPA via food ingestion during gestation; 2) fostering all pups at birth to eliminate effects of BPA on maternal behavior; 3) behavior tests conducted during the pre-pubertal period; and 4) production of lineages with either both parents from the same diet-lines, or parents from opposite F1 lineages.

Our focus is on social behaviors. Using three social behavior tests we have found differences between control and BPA-exposed mice of both sexes in F1, F3 and F4 lineages. One of the behavioral assays is social recognition. In this test the subject is presented with a novel adult ovariectomized mouse for one minute intervals, each presentation is separated by 9 minutes. Over the course of 8 presentations the subject's interest in the now familiar mouse wanes. This part of the test is the "habituation" period. On the final trial of the session the familiar mouse is replaced with a new ovariectomized adult and interest in the new mouse is greater than in the familiar mouse. This is referred to as "dishabituation." In F1 mice gestational exposure to BPA elevates investigation during the habituation phase. This difference is also noted in F3 mice. In addition F3 mice do not display dishabituation to the novel female. To ask if this transgenerational effect on behavior is transmitted via male or female germ cells, we compared behavior in control and BPA lineage mice to those from mixed lineages, in which either the dam or the sire was from the BPA line and the other parent from the control line. These data show that the actions of BPA on habituation require both parents from BPA lines; however, the effect on dishabituation only requires that the maternal lineage was exposed to BPA.

Our hypothesis is that behavioral effects are caused by stable differences between control and BPA-exposed lineages in histone modifications, which in turn change gene expression in brain. We use an unbiased approach to find these modifications and their affected genes. Analyses of RNA-sequencing data sets comparing active transcripts in the preoptic area and bed nucleus of the stria terminalis are ongoing and preliminary data will be shared.

Both genes and environment influence the expression of behaviors. Our data show that BPA is one of the many environmental factors and that heritable effects of EDCs also have important implications for complex neurobehavioral diseases.

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Reference(s):

Abstract type: Basic Research
Category: Nervous System
Keywords: Epigenetics, Prenatal, Transgenerational

Presented in Session: Plenary II: Trans-generational inheritance
Date/Times: Monday, October 27, 1:30-3:00 PM

Developmental exposure to 2,3,7,8,-tetrachlorodibenzo-p-dioxin (TCDD) has implications for multi- and transgenerational effects on antiviral immunity

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Recent studies reveal that maternal exposures can change biological processes and contribute to disease across generations; however, few studies have focused on multi- and transgenerational effects of developmental exposure on the function of the immune system. The work reported here presents a new study designed to directly address this knowledge gap by examining how developmental exposure perturbs the function of the immune system across generations. A properly tuned immune system is critical to public health, as it provides our main defense against infectious diseases. One category of chemicals for which there is evidence that developmental exposure perturbs immune function in humans and animal models is aryl hydrocarbon receptor (AHR) ligands. For instance, developmental exposure to the prototype AHR ligand, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), disrupts the immune response to influenza A virus in the F1 generation, including changes in T lymphocyte responses and pulmonary inflammation. In this study we determined whether the same immunological changes in the F1 generation are observed in the F2 generation, with the long-term goal of extending this comparison to comprehensively characterize developmental (F1), multigenerational (F2), and transgenerational (F3) modifications to the response of specific immune cells. Compared to offspring of control dams, there were fewer virus-specific CD8+ cytotoxic T lymphocytes (CTL) in the lung-draining lymph nodes (MLN) and lungs of infected TCDD-exposed F1 mice. The response to infection was also different from control lineage in exposed F2 mice; however, rather than diminution, there were more virus-specific CD8+ T cells in the lung, and no significant difference in lymph nodes. In exposed F1 mice, the response of CD4+ T cells to infection was skewed, such that frequency of conventional helper subsets was diminished, but the percentage of regulatory CD4+ (Treg) cells was increased in MLN. Yet, the number of all CD4+ T cell subsets in lungs of infected F1 mice was enhanced in offspring of TCDD-treated dams. Like the F1 generation, more CD4+ T cells were detected in the lungs of infected F2 mice. Our data reveal that developmental exposure to TCDD caused persistent changes in immune function in both the F1 and F2 generations; however, the direction of change was not always the same from one generation to the next. Regardless of the direction of change, these data suggest that developmental exposure causes the immune system to become unbalanced, which likely has broad consequences on host defenses against common pathogens, and may influence overall health across generations.

Source(s) of support:

Reference(s):

Abstract type: Basic Research
Category: Immune System
Keywords: Prenatal, Transgenerational

Presented in Session: Plenary II: Trans-generational inheritance
Date/Times: Monday, October 27, 1:30-3:00 PM

Trichloroethylene-induced epigenetic changes in T cell functions

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The industrial solvent trichloroethylene (TCE) has ended up as a major water pollutant in the USA and around the world. Previous studies have shown that chronic (32-week) exposure to low-level concentrations of TCE in the drinking water of female MRL+/+ mice promoted liver inflammation and autoantibody production commensurate with autoimmune hepatitis. This was accompanied by the expansion of CD4+ T cells that secreted increased levels of IFN-gamma and expressed an memory effector (CD44hiCD62Llo) phenotype. The current 40-week longitudinal study was conducted to determine the mechanism by which TCE altered CD4+ T cell function. Transcriptomics and associated pathway analysis indicated that TCE effects in the activated/memory CD4+ T cells focused on IFN-gamma□□□□Subsequent bisulfite sequencing of individual CpG sites in the Ifng promoter revealed that TCE induced biphasic alterations in DNA methylation in CD4+ T cells that paralleled gene expression. These alterations were CD4+ T cell subset-specific and time-dependent. TCE also altered memory CD4+ T cell expression of genes used to assess global effects on DNA methylation, namely retrotransposons Iap (Intracisternal A Particle) and Muerv (murine endogenous retrovirus). Thus, for the first time, a toxicant known to promote autoimmune disease has been shown to alter epigenetic processes (DNA methylation) in the cell type that mediates pathology, namely activated/memory CD4+ T cells.

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Reference(s):

Abstract type: Basic Research
Category: Immune System
Keywords: Epigenetics, Experimental Models, Mechanisms & Pathways

Presented in Session: Breakout 3: Effects of developmental exposures on immune functions
Date/Times: Monday, October 27, 3:30-5:00 PM

Immune dysfunction in children with prenatal immunotoxicant exposures

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The immune system of the fetus and neonate develops extensively, and a normal maturation of the immune system is dependent upon specific processes that occur at different time points and in different body compartments. This makes the early-life immune system a moving toxicological target for xenobiotic interactions. Adverse outcomes after exposure to immunotoxicants are immune dysfunction and misregulation. Exaggerated responses may lead to increased risk of allergic or autoimmune diseases, whereas immunosuppression may give an increased risk of infections and cancer.

Several human studies have reported associations between prenatal exposure to immunotoxicants like polychlorinated hydrocarbons (PCB), dioxin and perfluoroalkyl substances (PFAS) and immune-related health outcomes in childhood, such as increased risk of infections and/or wheeze in early life. In addition, a negative association has been observed between prenatal exposure to these immunotoxicants and antibody responses to childhood vaccines. These findings are indicative of immunosuppression, and a cause-effect relationship has been supported by animal studies.

In a Norwegian birth cohort study, prenatal exposure to PCB and dioxin was found to be positively associated with increased risk of common cold and negatively associated with vaccination responses against measles in the children at age 3 years. Whole-genome gene expression analyses were performed in cord blood from these children. Several immune-related genes were found to correlate significantly with both exposure to PCB and dioxin and with measles vaccination responses, such as genes involved in T cell activation and proliferation and genes in the HLA system. These findings of gene expression modulation after exposures to PCB and dioxins, lend support for an immune modulation that may affect immune functionality in childhood.

Source(s) of support:

Reference(s):

Abstract type: Clinical Research
Category: Immune System
Keywords: Birth Cohort, Prenatal, Immunotoxicology

Presented in Session: Breakout 3: Effects of developmental exposures on immune functions
Date/Times: Monday, October 27, 3:30-5:00 PM

Early life environmental exposures and reduced response to infant tuberculosis vaccination

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BACKGROUND
The incidence of pediatric tuberculosis remains high in numerous countries, despite BCG vaccination. The reasons for the diminished effectiveness of the BCG vaccine are multifaceted and poorly understood. Exposure to environmental chemicals may play a role in decreased immunity and have been associated with lower immune responses to other vaccines. To examine whether environmental exposures decrease the infant BCG vaccine response, we examined two prevalent environmental pollutants, PCBs (polychlorinated biphenyls) and, DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene), the main metabolite of DDT, in relation to 6-month infant BCG-specific antibody levels.

METHODS
Data came from families participating in a prospective birth cohort in eastern Slovakia. At birth, maternal and cord blood were collected for chemical analyses, and infants were immunized with BCG. At 6 months of age, 86% of families followed up, and blood was collected from infants for chemical analyses and to determine BCG-specific IgG and IgA levels. Multivariable linear regression models were fit to examine chemical—BCG associations among 445 mother-infant pairs, with adjustment for confounders.

FINDINGS
The median 6-month infant concentration of PCB-153, a prevalent PCB congener, was 119 ng/g lipid (IQR: 38, 252) and 388 ng/g lipid (IQR: 115, 861) for DDE. Higher infant concentrations of PCB-153 and DDE were strongly associated with lower BCG-specific IgG and IgA levels. For instance, after adjustment, BCG-specific IgG levels were 45% lower for infants with DDE concentrations at the 75th percentile of exposure compared to the 25th percentile (95% CI: -53, -37; $p<0.0001$). Results were similar in magnitude and precision for PCB-153.

CONCLUSIONS
The observed associations in this study indicate that environmental chemical exposures may be an overlooked contributor to poorer responses to BCG vaccine. Furthermore, these findings may have particular implications for countries where DDT is used for malaria vector control and tuberculosis rates are high. The overall association between these exposures and tuberculosis incidence is unknown.

Source(s) of support:
Reference(s):

Abstract type: Population Research
Category: Immune System
Keywords: Birth Cohort, Epidemiology, Postnatal

Presented in Session: Breakout 3: Effects of developmental exposures on immune functions
Date/Times: Monday, October 27, 3:30-5:00 PM

Fetal hematopoietic stem cells are the coalmine canaries portending adverse later-life immune outcomes

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Self-renewal is the critical process by which undifferentiated hematopoietic stem cells perpetuate themselves throughout life while also maintaining potential to differentiate into an array of blood cell lineages. This process is established during development in response to microenvironmental signals provided by the different anatomical locations in which hematopoietic stem cells (HSC) traffic through. Alterations in responsiveness to these microenvironmental signals may lead to perturbations in energy regulation, migration and establishment of self-renewal, potentially impacting a spectrum of later-life blood diseases ranging from stem cell exhaustion to hematological malignancies. Among the known physiological regulators of hematopoiesis that potentially connect environmental exposures to later-life immune disease is the aryl hydrocarbon receptor (AHR) due to its affinity for structurally related halogenated aromatic contaminants such as 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD). Given the known role of the AHR as a critical regulator of HSC homeostasis we hypothesized that developmental exposure to TCDD displaces the AHR from its self-renewal regulatory function leading to changes in energy regulation and long-term alterations in immune system development. To test this hypothesis we exposed pregnant mice to 3μg/kg TCDD and then used a two-pronged approach of first analyzing fetal HSCs phenotypically and functionally and secondly, we measured changes in the progeny of HSCs by following Notch-1 dependent T-cell differentiation in adult mice. Analysis of fetal HSCs following developmental exposure TCDD revealed an increase in reactive oxygen species, a decrease in ATP production, and increased mitochondrial autophagy. These alterations in HSC homeostasis were accompanied by a more than 50% reduction in the functional capacity of TCDD-exposed HSCs to compete with naive HSCs in competitive reconstitution assays. This failure of HSCs to compete in reconstitution assays indicates developmental AHR activation impairs long-term self-renewal. Furthermore, we found that in adult progeny of fetal HSCs, Notch1-dependent signal transduction is attenuated in T-cells obtained from mice developmentally exposed to TCDD. Taken together, these results demonstrate that AHR activation by TCDD in fetal HSCs has both immediate- and long-term consequences for hematopoiesis and immune system homeostasis. From these data we suggest that fetal HSCs have the potential to be utilized as an indicator cell type for predicting later-life immune system dysfunction following changes to the intrauterine environment.

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Reference(s):

Abstract type: Basic Research
Category: Immune System
Keywords: Experimental Models, Mechanisms & Pathways, Prenatal

Presented in Session: Breakout 3: Effects of developmental exposures on immune functions
Date/Times: Monday, October 27, 3:30-5:00 PM

Birth cohort research as part of public health interventions

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In the early eighties we discovered that the Faroese population was highly exposed to methylmercury and shortly afterwards, POPs, PCB and DDE levels also appeared to be very high in the blood of mothers we tested. The source was mainly the traditional consumption of a sea mammal – the pilot whale.

A pilot study in the mid-eighties revealed a high range of contaminants in fertile women, therefore a birth cohort study was considered feasible in order to elucidate the possible health effects of prenatal exposure to mercury. Hence the first birth cohort was established in 1986/87 comprising 1023 mother-child pairs. Eventually it became obvious that a detailed description of the co-exposure with POPs was needed leading to establishment of additional birth cohorts in 1994, 1997-2000 and 2008-2010. More than 2300 are now included and are repeatedly followed up – the oldest now 27 and the youngest 5 years of age. The central nervous system and the immune system have been our main focus in analysing the effects of these contaminants.

In such examinations the cohort members are contacted repeatedly over the years, and our research hypothesis and findings are communicated thoroughly. Since the total number of participants in these cohorts is a relatively large part of the total population of young people the impact on the society by this direct personal communication to cohort members is quite significant. Furthermore, these ongoing studies in such a small society creates media awareness, which creates an opportunity to communicate the public health message about the negative health effects of the contaminants. This continual communication, including increasingly restrictive dietary recommendations has led to a dramatic reduction in the exposure levels among the cohort mothers – and not because of a decrease in the marine pollution, but because the mothers have followed our dietary recommendations, based on the effects found in the cohort studies.

In 2008 the Chief Medical Officer of the Faroes recommended that pilot whale was no longer used for human consumption as a result of the results from our cohort research. Given the fact that pilot whales have been consumed for hundreds of years in this community and constitute an important part of the diet these recommendations must be considered a radical message regarding both diet and cultural identity.

We believe the reason so many mothers are following the dietary recommendations is because they are based on research produced from within this society, avoiding the uncertainty factor associated with applying findings from foreign societies. Furthermore the cohort research has been able to estimate the beneficial effects of seafood, i.e. of marine fat and selenium. We have not found that higher values of selenium had any protective effect against mercury. However, marine fatty acids do mask the negative effect of mercury on the central nervous system.

Source(s) of support:

Reference(s):

Weihe P, Debes Joensen H,Int J Circumpolar Health. 2012; 71

Abstract type: Population Research
Category: Nervous System
Keywords: Birth Cohort, Epidemiology, Public Health

Presented in Session: Breakout 4: Novel strategies for prospective birth cohorts
Date/Times: Monday, October 27, 3:30-5:00 PM

Strategies and results from the Japan Environment and Child Cohort

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The Japan Environment and Children's Study (JECS) is a longitudinal birth cohort study conducted by the Ministry of the Environment, the Government of Japan (1). The study started in January 2011 aiming to enrol 100,000 pregnant women during 3 years. The children born to the recruited mothers will be followed up until they reach 13 years of age. The National Institute for Environmental Studies is responsible for scientific conduct of the study, cooperating with other stakeholders, including other Ministries, local governments and international organisations. Fifteen Regional Centres, which are seated in universities, are responsible for recruiting study participants and conducting follow-up programs in respective study areas, collaborating with local governments.

In the study, the relationships between a broad range of the environment and children's health and development will be examined. The main emphasis will be given to the effects of environmental chemicals such as persistent organic pollutants, metals, endocrine disruptors, agrichemicals, personal care products as well as genetics, socio-economics and lifestyles. The exposure assessment will involve the measurement of target chemicals in biological specimens (blood, urine, breast milk and hair) as well as in the household environment; simulation models based on air and water quality monitoring data; exposure models using market basket survey and household measurement data and questionnaires. Other environmental stressors such as socioeconomic development (e.g. education, employment, house-hold income, social capital, and community support), lifestyle factors (stress levels, diet, smoking and alcohol habits, physical exercise activities, sleep, infections, and medications), and physical environment (heat, ionizing radiation, housing condition, and neighborhood) will also be measured. JECS' priority outcomes include reproduction/pregnancy complications, congenital anomalies, neuropsychiatric disorders, immune system disorders, and metabolic/endocrine system disorders.

The participant enrolment was completed on 31 March 2014, reaching 103,106 registrations. As of 1 September 2014, over 90,000 babies were born. Biochemical tests of the blood samples collected during pregnancy have been done for more than 90,000 samples. This year 20,000 blood samples are being analysed for elements such as lead, cadmium, mercury, manganese and selenium. Urinary nicotine metabolites will also be measured this year.

Source(s) of support:

Reference(s):

(1) Kawamoto T et al., BMC Public Health 2014; 14:25.

Abstract type: Population Research
Category: Other: Multiple systems
Keywords: Birth Cohort, Epidemiology, Exposure Assessment

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Date/Times: Monday, October 27, 3:30-5:00 PM

Prenatal exposure to stress modifies the association between prenatal lead and infant neurodevelopment

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Background Prenatal exposures to lead and to stress have been individually associated with infant neurodevelopment, but few epidemiological studies have looked at their co-exposure in humans, especially in a prospective design. We examined if the simultaneous exposure to lead and stress in the prenatal period is associated with neurodevelopment in 12-24 month old infants.

Objectives We examined if exposure to stress during gestation modified the association between prenatal lead exposure and neurodevelopment in infants aged 12-24 months.

Methods Using the Bayley-III scales for infant neurodevelopment we evaluated cognitive, language and motor scores at 12, 18 and 24 months for 690 infants from the Programming Research in Obesity, GRowth, Environment and Social Stressors, Mexican birth cohort. Maternal blood lead levels were obtained during the second and third trimester and at birth, and cortical bone measurements were obtained at one month postpartum. Maternal psychosocial stress was measured as negative life events (NLE) using the Crisis in Family Systems-Revised questionnaire during pregnancy. We explored the associations for each prenatal lead indicator and prenatal stress, with 12 and 24 month Bayley scores separately using multivariate regression models. We evaluated effect modification with models that included an interaction term lead x stress (dichotomized with a cut-point of 3 or more NLEs) and with models stratified by stress.

Results The association between prenatal lead exposure and neurodevelopment scores differed by prenatal stress category and was significant only for the 12 month evaluation. For the three scales (cognitive, language and motor) increased lead exposure was associated with lower scores in the high prenatal stress category. The interaction between lead and stress was statistically significant ($p = 0.03$) for tibia lead in the cognitive scale, for 2nd ($p = 0.03$) and 3rd ($p = 0.05$) trimester blood lead in the language scale, and for the 3rd ($p = 0.03$) trimester blood lead in the motor scale. For children in the high stress category every µg/dl increase in 2nd and 3rd trimester blood lead, language and motor scores were reduced by half a point.

Conclusions Our findings suggest that stress modifies the effect of prenatal lead on infant neurodevelopment. Our results add to the existing evidence pointing at the importance of studying exposures as mixtures rather than single ones. In particular, our study is perhaps the first to prospectively assess lead and stress in pregnancy and determine whether they modify each other's effect on subsequent child neurodevelopment.

Source(s) of support:
Reference(s):

Abstract type: Population Research
Category: Nervous System
Keywords: Birth Cohort, Prenatal, Other: neurodevelopment

Presented in Session: Breakout 4: Novel strategies for prospective birth cohorts
Date/Times: Monday, October 27, 3:30-5:00 PM

Individual and joint association of exposure to ambient PM2.5 and ozone and maternal smoking with preterm birth in the Boston Birth Cohort

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BACKGROUND: Preterm birth is a major risk factor for infant mortality and morbidity. Joint associations of ambient PM2.5 (particulate matter with a diameter ≥2.5μm) and cigarette smoke with risk of preterm birth and gestational age at birth have not been adequately explored.

OBJECTIVE: To investigate individual and joint associations of PM2.5 and smoking with preterm birth (<37 weeks of gestation) and gestational age in 2759 mothers (421 preterm and 2338 term births) in the Boston Birth Cohort.

METHODS: Maternal exposure to ambient PM2.5 was based on measurements from the closest U.S. Environmental Protection Agency air monitoring station. The odds ratios of preterm birth and 95% CI were estimated using multilevel logistic regression. The effect on gestational age was investigated using multiple linear regression.

RESULTS: Controlling for season, maternal race/ethnicity, body mass index, age, and education level, and ambient ozone level at corresponding time points, mothers in the lowest PM2.5 exposure quartile in the third trimester of their pregnancies had a lower risk of preterm birth compared to mothers in the second (OR=1.43 [95% CI: 0.99, 2.07]), third (OR=1.87 [95% CI: 1.31, 2.67]), and fourth exposure quartiles (OR=2.55 [95% CI: 1.80, 3.61]). Consistent with these results, gestational age at birth was highest in mothers in the lowest quartile of exposure to PM2.5 during the third trimester of their pregnancies compared to gestational age at birth among mothers in the second (β= -0.13 [SE: 0.13, p=0.33]), third (β= -0.19 [SE: 0.13, p=0.14]), and fourth exposure quartiles (β = -0.53 [95% CI: 0.13, p<0.001]). A linear trend test was significant (p<0.001) for all trimesters. In a stratified analysis, these effects were enhanced in mothers who smoked during pregnancy and were exposed to concentrations of PM2.5 ≥ 12 ug/m3 , compared to mothers who did not smoke and were exposed to PM2.5 < 12 ug/m3. The joint effects of maternal smoking during pregnancy and exposure to PM2.5 in the second trimester, third trimester, last month before delivery, and last two weeks before delivery were additive and in some cases more than additive. For example, gestational age at birth was decreased by -1.25 weeks in mothers who were both exposed to PM2.5 ≥ 12 ug/m3 in the third trimester and who smoked during pregnancy, compared to decreases of -0.38 and -0.64, respectively, among mothers exposed to high PM2.5¬ levels or cigarette smoke alone.

CONCLUSIONS: In this study, there was a dose-response relationship between maternal exposure to ambient PM2.5 quartiles and risk of preterm birth. The joint effects of maternal exposure to ambient PM2.5 and maternal smoking on gestational age exceeded the individual effects of exposure to each pollutant alone. Studies that consider only the individual contributions of exposure to indoor and outdoor pollutants might underestimate the risk of preterm birth in subpopulations with multiple sources of exposures.

Source(s) of support: The Boston Birth Cohort (the parent study) is supported in part by the March of Dimes PERI grants (20-FY02-56, #21-FY07-605); and the National Institutes of Health (NIH) grants (R21 ES011666, R01 HD041702, R21HD066471). We wish to acknowledge generous philanthropic support from The Ludwig Family Foundation; the Zanvyl Krieger Endowment.

Reference(s):

Abstract type: Population Research
Category: Other: Preterm Birth
Keywords: Birth Cohort, Epidemiology, Exposure Assessment

Presented in Session: Breakout 4: Novel strategies for prospective birth cohorts
Date/Times: Monday, October 27, 3:30-5:00 PM

Pre- and postnatal exposure to persistent pollutants and obesity

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Extensive multidisciplinary research efforts during the last few decades have led to the recognition of the impact that early life environmental influences may have in the development of severe chronic disease including obesity and cardiometabolic syndrome. Fetal and early postnatal life is considered to be the most vulnerable time period of the adverse health effects of environmental pollutants. Birth cohort studies with a clear temporal separation between exposure assessment and disease occurrence permit to establish causal direction of these associations and contribute importantly in elucidating the role of environmental pollutants on the development of obesity in humans. We have aimed to evaluate the association between early life exposure to persistent pollutants on early postnatal growth and obesity risk since the first year of life through childhood. The INMA-Birth Cohort Study is a network of seven cohort studies conducted at different Spanish regions following more than 2000 mother-child pairs since the first trimester of pregnancy through childhood (recruitment periods: 1997-2002 and 2003-2008). Exposure to persistent pollutants (DDT/DDE, HCB, PCBs) was measured in maternal serum samples collected at pregnancy and/or cord blood samples collected at birth, and postnatally at child serum samples collected from a subset of children. Rapid growth was defined as an age-and-sex-specific z-score change in weight >0.67 SDs in the first 6 months of life. Overweight at later ages up to 7 years was defined as a BMI age-and-sex-specific z-score ≥ the 85th percentile using the WHO Child Growth Standards. Prenatal exposure to persistent pollutants was associated with increased risks for early rapid growth and overweight since the first year of life and onwards. The relative risks for children exposed to the highests levels compared to children exposed to the lowest level (using tertile or quartile cutoffs) ranged from 1.30 to 1.60 ($P<0.05$). Multipollutant adjustment for simultaneous exposures and postnatal exposure to persistent pollutants did not influence these associations. Associations differed according to the pollutant and child age at outcome assessment. There was some evidence that child sex, breastfeeding duration, child high-fat diet and maternal prepregnancy overweight may influence the associations between some of the persistent pollutants studied and obesity related outcomes. Continuous follow-up is required to elucidate the persistence of these associations later in childhood, adolescence and adult life. Further research is much needed to identify the most critical windows of exposure susceptibility and the most susceptible population groups and to elucidate the underlying mechanisms and any potentially synergistic or antagonistic effects of multiple exposures to environmental pollutants on the development of obesity.

Source(s) of support:

Reference(s):

Abstract type: Population Research
Category: Obesity
Keywords: Birth Cohort, Epidemiology, Public Health

Presented in Session: Plenary III: Developmental exposures in obesity etiologies
Date/Times: Tuesday, October 28, 8:30-10:00 AM

Maternal exposure to BPA and obesity in the next generation

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There is mounting evidence to suggest a relationship between bisphenol A (BPA) exposure and obesity and metabolic disease in rodent models and in humans. Our studies in CD-1 mice exposed perinatally to BPA have revealed increased body weight and fat mass accompanied by associated metabolic complications later in life. Pregnant Dams were exposed to BPA from Gestational Day 8 through Lactation Day 16 via osmotic minipumps implanted under the skin. The pumps released continuous low levels of BPA over a three week period exposing offspring to BPA in utero and during lactation. The doses of BPA delivered included 0, 0.25, 2.5, 25, and 250 µg BPA/kg BW /day. Measurements of BPA levels in serum samples from the dams and their litters, were within the range reported in humans indicating that the doses being delivered were environmentally relevant.

The results of initial studies revealed a non-monotonic dose response to BPA exposure for the parameters being studied, with the 2.5 and the 25µg doses causing more pronounced effects than the 0.25 or 250µg BPA doses and as a result, subsequent studies concentrated on those doses. Male offspring exposed perinatally to 2.5 and 25 ug BPA showed increased body weight and developed a 12-26% increase in fat mass (as determined by MRI analysis) relative to controls when examined at time points from 10 through 24 weeks of age. By 13-15 weeks of age, evidence of altered glucose homeostasis was noted in BPA exposed males. When fed a 45% high fat diet (HFD), both BPA exposed and control males showed a similar percent increase in body weight and fat mass relative to their chow fed brothers and therefore these measurements did not reveal an obvious synergism between BPA exposure and HFD. In contrast, BPA exposed males eating a HFD, developed a marked hyperglycemia. At 14 weeks on diet, 36% of the 2.5 µg BPA and 50% of the 25 µg BPA males, but none of the control males or their chow fed brothers had fasting glucose levels above 350 mg/dl. Histological analysis of the gonadal fat pad in the males revealed evidence of increased inflammation in chow fed and HFD BPA exposed animals. Quantitative PCR studies demonstrated increased inflammatory cytokine expression in the gonadal fat pad that was most pronounced in the BPA exposed animals on the HFD. Early BPA exposure also promoted increased lipogenic gene expression and lipid accumulation in the liver. An increased expression of genes involved in cholesterol synthesis were observed in the BPA exposed males relative to controls, and measurements of Cholesterol and Nonesterified Fatty Acids (NEFA) were increased.

In summary, data from our studies reveal that early BPA exposure leads to increases in body weight and fat mass as well as other changes associated with metabolic disease in adulthood. Unfortunately, BPA is just one of a growing list of chemicals that may contribute to the alarming rise in obesity and its well documented complications.

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Reference(s):

Abstract type: Basic Research
Category: Obesity
Keywords: Exposure Assessment, Prenatal, Postnatal

Presented in Session: Plenary III: Developmental exposures in obesity etiologies
Date/Times: Tuesday, October 28, 8:30-10:00 AM

Integration of experimental and epidemiological approaches to developmental obesogenicity

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We recently concluded a European research project entitled "OBELIX" which combined experimental and epidemiological approaches to investigate if early life exposure to EDCs plays a role in the development of obesity and related disorders later in life. OBELIX investigated six major classes of EDCs, including dioxins, polychlorinated biphenyls, brominated flame retardants, organochlorine pesticides, phthalates, and perfluorinated alkyl acids (PFAAs). Main results included:

Exposure assessment: OBELIX demonstrated that perinatal exposure to major classes of EDCs is widespread across Europe. New methods were developed for the sensitive analysis of phthalate metabolites and PFAAs in cord blood and breast milk. Novel postnatal exposure models were developed, indicating divergent effects of pre- and postnatal exposure to EDCs.

Epidemiological studies in birth cohorts: health outcomes such as birth weight, growth, body mass index (BMI) and levels of serum hormones were analyzed in children. Postnatal exposure to PCB 153 was related to reduced birth weight, body mass index and serum leptin levels at 6 years. Prenatal DDE was associated with rapid growth in children up to 2 years, increased BMI and serum leptin levels at 6 years. Perinatal exposure to dioxin-like chemicals was associated with elevated BMI at 6 years. Experimental studies in mice: perinatal dietary exposure to BPA, PFOA, TCDD, DEHP and PFOA resulted in compound- and sex-specific effects on metabolic pathways in adulthood, such as altered serum lipid and adipokine levels. The effects on metabolic pathways did not consistently coincide with increased body weight or adiposity. In vitro studies with a mouse preadipocyte differentiation model indicated that EDCs induce fat cell differentiation, alter adipogenic gene expression and change in global DNA methylation, as well as alter methylation of specific genes such as PPARg.

Risk assessment: for BPA and PFOA, critical effect concentrations (CECs) in animal studies were lower than those used to set current tolerable daily intake levels, indicating that current TDIs may not be sufficiently protective for metabolic effects. Importantly, health outcomes measured in children were often observed at lower exposure levels than CECs in animal experiments. This may be due to species differences or to combined exposures of the human population. Taken together, the results of the OBELIX project indicate that early life exposure to EDCs can alter metabolic pathways that play an essential role in energy metabolism and weight regulation. Current studies are underway with alternative (zebrafish) models as rapid screens for new obesogenic chemicals, as well as to study transgenerational effects of developmental obesogen exposure.

This project received funding from the European Community's Seventh Framework Programme under grant agreement OBELIX n° 227391, and the Netherlands Science Foundation [VIDI/864.09.005].

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Reference(s):

Abstract type: Basic Research
Category: Obesity
Keywords: Birth Cohort, Experimental Models, Exposure Assessment

Presented in Session: Plenary III: Developmental exposures in obesity etiologies
Date/Times: Tuesday, October 28, 8:30-10:00 AM

Prenatal phthalate exposures and body mass index among 4 to 7 year old children: A pooled analysis

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Background and Aims: Phthalate exposures, especially during fetal development, are hypothesized to be obesogenic. Effects may differ by sex for phthalates with anti-androgenic activity. Previous studies of phthalate exposures and body size are primarily cross-sectional and none examined gestational exposures, a relevant exposure period for developmental programming of obesity. We assessed associations between maternal urinary phthalate biomarkers during pregnancy and body mass index (BMI) and overweight or obese status during childhood in three prospective birth cohorts.

Methods: The study sample included 708 children from the Cincinnati (n=218), Columbia (n=339), and Mount Sinai (n=151) Children's Environmental Health Center birth cohorts who had third trimester maternal urinary phthalate metabolite concentrations and height and weight data collected at ages 4 to 7 years (total number of visits=1415). At each follow-up visit, we calculated BMI z-scores and classified children as overweight/obese if their BMI was greater than or equal to the 85th percentile for age and sex. We estimated associations between standard deviation increases in natural log phthalate metabolite concentrations and BMI z-scores or overweight/obese status using multilevel linear or logistic regression with random intercepts, respectively. We adjusted associations for maternal sociodemographics, height, pre-pregnancy BMI, and smoking during pregnancy; urine dilution and collection date; gestational weight gain; breastfeeding; child sex and age at follow-up; and pooled analyses were also adjusted for cohort. Finally, we accounted for confounding by correlated phthalate metabolites by assessing associations in multiple metabolite models.

Results: Mono-3-carboxypropyl phthalate (MCPP) was associated with increased odds of overweight/obese status at follow-up (OR = 1.8, 95% CI = 1.1, 3.1). Mono-ethyl (MEP) and mono-benzyl (MBzP) phthalate were inversely related to overweight/obese status, though CIs included the null (MEP: OR = 0.7, 95% CI = 0.4, 1.1; MBzP: OR = 0.7, 95% CI = 0.4, 1.2). Whereas associations of phthalate metabolites with overweight/obese status did not differ by child sex, associations of certain phthalate metabolites with BMI z-scores differed in girls and boys. MEP was negatively associated with BMI z-scores in girls (pooled β = -0.16, 95% CI= -0.30, -0.02) but not among boys (pooled β = 0.05, 95% CI = -0.09, 0.19). Associations of mono-n-butyl phthalate, MCPP, and summed di(2-ethylhexyl) phthalate metabolites with BMI z-scores were also significantly different among girls and boys, though 95% CIs included the null for both sexes. We did not observe modification of any associations by cohort. Conclusions: In this pooled study of three birth cohorts, MCPP was positively associated with overweight and obesity among 4 to 7 year old children.

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Reference(s):

Abstract type: Population Research
Category: Obesity
Keywords: Birth Cohort, Epidemiology, Prenatal

Presented in Session: Plenary III: Developmental exposures in obesity etiologies
Date/Times: Tuesday, October 28, 8:30-10:00 AM

Abnormalities of glucose metabolism in children exposed to diabetogenic environmental chemicals

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Not provided.

Source(s) of support:
Reference(s):

Abstract type: -
Category: Diabetes & Metabolism
Keywords:

Presented in Session: Breakout 5: Developmental exposures and diabetes pathogenesis
Date/Times: Tuesday, October 28, 10:30 AM - 12:00 PM

Prenatal air pollution exposure induces sexually dimorphic fetal programming of metabolic outcomes in adult offspring

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Obesity is now epidemic worldwide, and it is becoming clear that diet and exercise alone are not sufficient to explain its increased prevalence. Emerging evidence suggests that environmental chemical exposures during critical windows of development may contribute to the escalating prevalence of obesity and its associated diseases (e.g., type II diabetes) via long-term "programming" of the endocrine and/or immune systems. We tested the hypothesis that prenatal exposure to air pollutants would predispose offspring to exacerbated weight gain and metabolic abnormalities upon exposure to a high-fat diet in adulthood. Time-mated mouse dams were intermittently exposed to respiratory instillations of either a control substance (vehicle, VEH) or 50 µg diesel exhaust particles (DEP) every 3 days from embryonic day (E)2-17. Once adults, male and female offspring from both treatment groups were fed either a low-fat diet (LFD) or high-fat diet (HFD) for 9 weeks. Following HFD, DEP males gained significantly more weight, were insulin-resistant and more hyperinsulinemic than VEH males, despite no significant differences in activity level or food intake. Interestingly, there were no significant differences between DEP and VEH females on HFD. Both VEH and DEP offspring on a HFD exhibited increased expression of CCR2, a marker of monocyte infiltration, in their adipose tissue; however, only male DEP offspring exhibited increased levels of CD11b gene expression indicative of increased monocyte/macrophage activation. In parallel to this macrophage infiltration of the adipose tissue, which is a well-documented phenomenon in many animal models of obesity and insulin resistance, we uncovered a similar pattern occurring in the brains of the same animals. Both VEH and DEP offspring on a HFD had higher numbers of infiltrating CD11b+CD45high cells in their brains overall, but only in the hypothalamus of DEP male offspring did these cells express higher levels of CD11b on a per-cell basis. Behavioral tests revealed that these male DEP offspring also exhibited increased anxiety-like behavior, which has been associated with neuroinflammation in other models, after only 4 weeks on HFD. In order to determine if peripheral immune cells are functionally "primed" long-term by prenatal DEP exposure, we next administered an immune challenge (lipopolysaccharide, LPS) to VEH and DEP offspring at postnatal day (P)30 (165 µg/kg, i.p.). Two hours following LPS challenge, DEP male offspring had significantly higher levels of interleukin-1β in their serum than VEH male offspring, whereas female offspring did not significantly differ due to prenatal treatment. In conclusion, prenatal air pollution exposure "programs" offspring for increased susceptibility to diet-induced weight gain, insulin resistance, and neuroinflammation in adulthood in a sexually dimorphic manner.

Source(s) of support: U.S. Environmental Protection Agency Children's Environmental Health Center award RD 83329301 awarded to RLA; Research Incubator award from the Duke Institute for Brain Sciences awarded to SDB; National Science Foundation graduate research fellowship awarded to JLB.

Reference(s):

Abstract type: Basic Research
Category: Diabetes & Metabolism
Keywords: Experimental Models, Mechanisms & Pathways, Prenatal

Presented in Session: Breakout 5: Developmental exposures and diabetes pathogenesis
Date/Times: Tuesday, October 28, 10:30 AM - 12:00 PM

Maternal smoking during pregnancy and offspring type 1 diabetes mellitus risk – accounting for HLA haplotype

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BACKGROUND: There are indications that maternal smoking during pregnancy is associated with a decreased risk for their children to develop type 1 diabetes (T1D), however, earlier studies have not accounted for the genetic risk of the disease. AIMS: The main objective of this study was to study the risk of type 1 diabetes mellitus (T1D) in children exposed to tobacco smoking in utero, also taking genetic predisposition as expressed by HLA haplotype into account.

METHODS: In Skåne, the southernmost county of Sweden, all children who develop T1D are registered. During the years 1999-2005, 84 039 children were born in Skåne and by 1st of May 2013, 344 of those had developed T1D. For each child with T1D, three control children, matched for HLA haplotype and birthyear, were selected from the Diabetes Prediction in Skåne study, a prospective study where children from the general population born in Skåne during 2000-2004 were invited to participate. Information on prenatal smoking exposure was retrieved from a regional birth register. Conditional logistic regressions were used to evaluate T1D risk following prenatal smoking exposure.

RESULTS: Maternal smoking in early pregnancy was associated with a higher risk of the child developing T1D (odds ratio [OR] 2.83; 95% confidence interval [CI]: 1.67-4.80] for 1-9 cigarettes/day, and OR 3.91; 95% CI: 1.22-12.51] for >9 cigarettes/day. CONCLUSION: When genetic predisposition in terms of HLA haplotype was taken into account, we found that children exposed to smoking during fetal life were at higher risk of developing T1D in childhood.

Source(s) of support:

Reference(s):

Abstract type: Basic Research
Category: Diabetes & Metabolism
Keywords: Epidemiology, Prenatal, Transgenerational

Presented in Session: Breakout 5: Developmental exposures and diabetes pathogenesis
Date/Times: Tuesday, October 28, 10:30 AM - 12:00 PM

Developmental exposure to the endocrine disruptor tolylfluanid alters energy metabolism in adult mice

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Obesity and diabetes rates have increased dramatically over the last three decades, and increasing evidence implicates environmental exposure to synthetic chemicals in the pathogenesis of this metabolic disease epidemic. Tolylfluanid (TF) is a phenylsulfamide fungicide used on fruit crops in agricultural regions outside of the United States and as a booster biocide in marine paints. Previous work has shown that TF promotes adipocyte differentiation and adipocytic insulin resistance, likely through stimulation of glucocorticoid receptor signaling. More recent work demonstrated that chronic dietary exposure to this metabolic disruptor promotes adipose accretion and metabolic dysregulation, including insulin resistance and altered adipose physiology. The present studies examined the effects of in utero and lactational exposure on metabolic outcomes in mice. Female mice were exposed to TF in the diet at an approximate concentration of 100 mg/kg of chow from the time males were introduced into the cage until the pups were weaned. Despite no effect on litter size or female-to-male ratio, male and female pups born to TF-exposed mice had reduced body weight at weaning. Upon weaning offspring were housed in same-sex, littermate pairs and fed a normal chow diet for 16 weeks. Intraperitoneal glucose tolerance tests performed at 10 weeks of age revealed impaired glucose tolerance in male mice and a trend toward impairment in female mice. Relative to controls, TF-exposed male mice exhibited a decrease in the homeostatic model assessment (HOMA) of beta cell function (HOMA-B), suggesting impairments in beta cell function as the central driver of impaired glucose handling. At 19 weeks of age, there was no difference in body weight between exposed and control mice. While chronic TF exposure in adults increases adiposity, mice exposed developmentally to TF did not exhibit any change in adiposity as a group. However, male mice exhibited a marked and exaggerated dichotomy in adiposity with one cage mate having a significant increase in adiposity while the other had similar adiposity to controls. These "TF-sensitive" mice had an increase in adipose mass in all three fat depots assessed (perigonadal, perirenal, and mesenteric). Moreover, TF-sensitive mice had decreased glucose tolerance, increased fasting insulin levels, and reduced insulin sensitivity (measured by HOMA-IR) relative to their cage mates. Interestingly, a similar dichotomization was not observed in female mice. These data suggest that developmental exposure to the fungicide TF promotes metabolic dysregulation in adulthood; however, further work is required to determine the factors responsible for differences in responses among cage mates and the mechanisms by which developmental insults can lead to discrepant perturbations in energy metabolism.

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Environment-wide association studies towards a more complete view of exposures in health and disease

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It is hypothesized that greater than 50% of complex disease risk is attributed to differences in an individual's environment, but we lack ways of investigating the exposome – the totality of exposure load that occurs throughout a lifetime – in disease risk. Further, we have yet to incorporate the exposome in genome-based investigations, such as genome-wide association studies (GWAS) to assess how environment modifies genetic risk for complex disease. A new model is required to discover environmental exposures, and how they interact with the genome, in disease.

Here, we discuss ways of to remedy this problem through a strategy known as the "Environment-wide association study" (EWAS), where investigators assess 100s-1000s of personal exposures simultaneously. Analogous to GWAS, we will show how multiple personal exposures can be assessed simultaneously in terms of their association with diseases such as type 2 diabetes (T2D), heart disease risk factors, preterm birth, and mortality in population-based cohots. In these studies, we show how an array of exposures ranging from pollutants, nutrients, and pesticides are associated with these diseases and have effect sizes that are comparable or exceed GWAS findings. We will discuss the hurdles, including biases such as reverse causality, confounding, and challenges of inferring independence in midst of the dense correlation structure of the exposome.

We outline and show preliminary findings that combine the exposome with genome to assess how genetic risk for disease may be dependent on environmental exposure, known as gene-environment interactions (GxE). Because searching for interactions requires prohibitively large sample sizes and hypothesis tests, we describe how to increase chances for discovery and replication by consideration of interactions between top EWAS and GWAS findings.

With EWAS, it is now possible to build a search engine to find environmental exposures in disease.

Source(s) of support: NIH NIEHS Career Development Award (K99 ES023504)

Reference(s):

1. Patel CJ, Ioannidis JP. Studying the elusive environment in large scale. J Am Med Assoc 2014;311(21):2173-4.

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Keywords: Epidemiology, Public Health, Computational biology

Presented in Session: Breakout 6: Challenges in improving exposure assessments
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Identifying cumulative exposures to chemicals in pregnant women – A non-targeted exposome approach

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Exposure to endocrine disrupting environmental chemicals during pregnancy can increase the risk of developmental adverse health effects. Large-scale biomonitoring surveys such as U.S. National Health and Nutrition Survey (NHANES) provide important information on the extent to which chemicals are present in humans, but are limited by an a priori selection of chemicals to analyze and only cover ~10% of the chemicals in commerce. Thus, exposome approaches have been proposed to evaluate a fuller extent of chemical exposures.

We piloted a non-targeted liquid chromatography tandem mass spectrometry method utilizing LC-QTOF/MS to analyze Environmental Organic Acids (EOAs) in eighty serum samples collected from 2nd trimester pregnant women from Northern California. Our method allowed simultaneous detection of 733 EOAs, which include phenols, pesticides, PFCs, and phthalates.

We detected 534 out of 733 EOAs, of which 402 had unique chemical formulas. On average, we found 167 chemical hits per participant (range 89 – 210). Phenols, phthalates, and pesticides were classes with the most detects. Phenols had the greatest variability in detection between individuals (range 32 – 88 detections, mean 60.3, standard deviation 7.6). We detected 117 chemicals in more than 50% of study participants, 80 chemicals in more than 75% of study participants, and 22 chemicals were detected in 100% of study participants. There were 57 chemicals for which we found one hit match among the tested participants, and these were mostly pesticides and pesticide metabolites (38 out of the 57). Among the 22 chemicals detected in 100% of study participants, NHANES targets 4 chemicals. Chemicals detected in all study participants but not targeted in NHANES include 4-Nitrophenol (phenol), propargite (pesticides), and mono-n-heptyl phthalate (phthalate metabolite) – many of which have limited toxicology and/or biomonitoring data.

We found pregnant women exposed to multiple EOAs, some which have not yet been monitored in large scale biomonitoring studies. Further efforts are warranted to understand health effects of these chemicals for implications to health policy.

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Category: Other: Environmental exposures
Keywords: Epidemiology, Exposure Assessment, Prenatal

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Urinary concentrations of polycyclic aromatic hydrocarbons in Israeli adults: Demographic and life-style predictors

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Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants associated with adverse health outcomes, including cancer, asthma, and reduced fertility. Because data on exposure to these contaminants in Israel and the Middle East are very limited this study was conducted to measure urinary levels of PAHs in the general adult population in Israel and to identify demographic and life-style predictors of exposure.

We measured concentrations of five PAH metabolites: 1-hydroxypyrene (1OH_pyrene) and four different hydroxyphenanthrenes (1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene), as well as cotinine in urine samples collected from 243 Israeli adults from the general population. We interviewed participants using structured questionnaires to collect detailed demographic, smoking and dietary data. For over 99% of the study participants, urinary concentration of at least one of the PAHs was above both the limit of detection (LOD) and the limit of quantification (LOQ). All PAHs were significantly correlated (rho=0.67-0.92). Urinary concentration of hydroxyphenanthrenes, but not 1OH_pyrene, was significantly higher among Arabs and Druze study participants (N=56) compared to Jewish participants (N=183). For 4-Hydroxyphenanthrene, concentration in Arabs and Druze was 1.95 (95% CI 1.50-2.52) that of Jews, after controlling for creatinine, age and cotinine levels. Urinary concentrations of all PAHs were significantly higher among current smokers or participants with higher cotinine levels and increased significantly with smoking frequency. While PAHs levels were not associated with cotinine levels in nonsmokers in the overall study population, PAHs concentration was significantly higher among nonsmoking Jews with cotinine levels ≥ LOQ (1µg/L) , which represents exposure to environmental tobacco smoking, compared to nonsmoking Jews with cotinine levels< LOQ, with the highest ratio for 1OH_Pyrene (R=2.38, 95% CI 1.47-3.85). Among nonsmoking Arabs and Druze, higher hydroxyphenanthrenes concentrations were found for those consuming grilled food once a month or more. For 3-Hydroxyphenanthrene, concentration in those consuming grilled food once a more or was 2.72 (95% CI 1.01-4.98) times that of those consuming grilled food less than once a month or not at all, after controlling for creatinine, age and cotinine levels.

In conclusion, we found that the general adult population in Israel is widely exposed to PAHs. Exposure differed by ethnic sub-groups both in magnitude and sources of exposure. The finding of higher exposure among Arabs and Druze highlights the variability of environmental exposures across subpopulations and suggests that further research and preventive measure are warranted to reduce PAHs exposure and associated health outcomes, especially in the Arab population in the Middle East.

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Keywords: Epidemiology, Exposure Assessment, Public Health

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Derivation of cumulative toxicity indicators for indoor semi-volatile organic compounds: the case of reprotoxic and neurotoxic mixtures

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Semi-volatile organic compounds (SVOCs) are widely used indoors in consumer products, furniture or building materials and are also produced by combustion processes. They include a large panel of different compounds such as phthalates, polybrominated diphenyl ethers or pyrethroids. These uses can lead to human exposure to numerous molecules via oral, respiratory or dermal routes because of their physico-chemical properties. Indeed, their low to medium volatility yields adsorption in dust or particles, and presence in air. Most of SVOCs are suspected to have reprotoxic or neurotoxic properties but little is known on the health impact on SVOC mixtures. In order to investigate this impact, a cumulative health risk assessment is needed. This project aims at deriving cumulative toxicity indicators for reprotoxic and neurotoxic SVOCs present in indoor French dwellings. Methods employed are based on the dose-additivity assumption. Compounds were selected since they were detected in more than 10% of French dwellings. They were grouped according to a common effect or a common mode of action linked with reproductive and neurologic effect. Then, dose-response relationships were collected from a literature review and selected if meeting comparability criteria in terms of species, exposures (doses, route and duration) and windows of vulnerability. Benchmark doses (BMD) were derived using the PROAST software (RIVM, 2014) according to the Hill equations largely used in the modelling of continuous data.

Fifty-one SVOCs were selected among 66 measured. Twenty-seven have reprotoxic properties and for 17 SVOCs, the mode of action is based on a decrease in serum testosterone concentrations. Twenty-seven have neurotoxic properties leading to neurobehavioral disorders and for 19, a neuronal impairment was identified. After restricting to comparable dose-response data, it was possible to derive BMDs and associated relative potency factors based on a decrease in serum testosterone concentrations in laboratory mammals for 6 reprotoxic SVOCs (DEHP, BBP, DEP, benzo(a)pyrene, cypermethrin and bisphenol A). In addition, 95% lower bound of BMDs were derived for 13 neurotoxic SVOCs (DEHP, benzo(a)pyrene, BDE-47, 99, 209, PCB52, 77, 153, deltamethrin, diazinon, chlorpyrifos-ethyl, lindane, dieldrine) having a common effect (neuronal mortality based on an in vitro decrease in cell viability). These BMDs could serve as a point of departure for risk assessment.

The originality of this work was the inclusion of SVOCs from different chemical families detected in French dwellings. The main limitation was the lack of comparable toxicological data in terms of dose level ranges, duration of exposure, species or cell line tested, and window of vulnerability.

These cumulative toxicity indicators enable a cumulative risk assessment. Assessing risks due to SVOCs will help targeting prevention measures through the identification of compounds and exposure media that lead to a greater risk.

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Novel approaches to assessing cognitive function in early infancy

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A key focus of our Children's Environmental Health Research Center at Illinois is to develop novel and innovative approaches that can be used to assess the impact of prenatal chemical exposures on cognitive development during early infancy. The goal is to identify approaches that are both sensitive to prenatal chemical exposures and predictive of continued associations between exposure and cognition at later ages. If such tests can be identified, this would allow researchers to determine at a much earlier stage of development if children exposed to chemicals in the prenatal period are at risk of long term cognitive deficits associated with that exposure. The methods we are using are adapted from basic research on infant cognition and assess core abilities including information processing speed, memory, and attention that are the building blocks of all cognitive functioning. We have selected some of the tests we are employing (e.g. visual recognition memory) because psychological research has shown that performance on these tests in infancy is predictive of cognitive ability later in childhood. We are also employing tests of cognitive abilities such as mental rotation and theory of mind–which are known to be altered in autism, but we are administering these tests at much earlier ages than more traditional tests of these abilities are administered. We hope that development and implementation of these methods will ultimately contribute to the earlier detection of autism. Lastly, reliable sex differences have been documented on some of the tests were are using (mental rotation, physical reasoning), which will allow us to evaluate at very early ages (e.g. 4-5 months) if prenatal exposure to endocrine disrupting chemicals disrupts normal sex differences in cognition. To accomplish these goals more effectively we are working with experts in the field of computer vision to develop new visible light eye-tracking technology that will automate data collection by allowing us to collect reliable looking time data from newborn and very young infants using a typical computer webcam.

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Presented in Session: Plenary IV: Developmental exposures and neurobehavioral disorders
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Air pollution and developmental neurotoxicity

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Air pollution is a suspected developmental neurotoxicant. Though in animals, inhalation of diesel exhaust and ultrafine particles results in elevated cytokine expression and oxidative stress in the brain and altered animal behaviour; studies in children exposed to traffic-related air pollutants during pregnancy or infancy, when the brain neocortex rapidly develops, have only preliminarily been related to cognitive delays. Children spend a large proportion of their day at school when traffic pollution peaks during the day. Many schools are located in close proximity to busy roads which increases the level of traffic-related air pollution in schools. There is currently very little evidence on the role of traffic-related pollution in schools on cognitive function, though high cognitive executive functions essential for learning develops steadily from 6 to 10 years of age. The brain regions related to executive functions such as working memory and attention, largely the prefrontal cortex and the striatum have shown inflammatory responses after traffic-related air pollution exposure. Results on developmental trajectories and functional MRI (fMRI) from the BREATHE (BRain dEvelopment and Air polluTion ultrafine particles in scHool childrEn) project will be presented. Funded by ERC.

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Reference(s):

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Keywords: Epidemiology, Exposure Assessment, Public Health

Presented in Session: Plenary IV: Developmental exposures and neurobehavioral disorders
Date/Times: Tuesday, October 28, 1:30-3:00 PM

Early-life lead exposure and vulnerability to Alzheimer's-like neurodegeneration

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Alzheimer's disease (AD) affects about 5 million patients in the USA. Recent data suggests that AD maybe the third leading cause of death in the USA. The etiology of this disease, particularly, the sporadic form of AD, which affects 95% of patients, remains unknown. The late onset pattern and the absence of a genetic causation factor for sporadic AD, suggest an environmental involvement. Another unknown for the etiology of the disease is the period of onset. Does AD result from old age or does it have an earlier beginning? In this presentation, we will discuss the various environmental, dietary, and metabolic risk factors that may contribute to AD pathogenesis. We will explore potential mechanisms that can transmit the impact of environmental exposures across the lifespan. We will particularly focus on gene environment interactions, namely epigenetic pathways.

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Presented in Session: Plenary IV: Developmental exposures and neurobehavioral disorders
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Prenatal synthetic glucocorticoids and multigenerational paternal programming of offspring behaviour and HPA function

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Synthetic glucocorticoids (sGC) are administered to pregnant women at risk for preterm labour to mature the fetal lungs. Use of multiple courses of sGC became routine in the late1990s and early 2000s. Subsequent studies in humans and animal models have linked multiple courses of sGC to behavioural disturbances and altered hypothalamic-pituitary-adrenal (HPA) function in children and young offspring. Emerging data suggest that these effects are multigenerational. Recent studies have demonstrated maternal transmission of altered behaviour and HPA function to young second generation (F2) offspring. In the present study, we hypothesized that prenatal sGC would result in increased activity and anxiety, and reduced attention and HPA response to stress in young F2 offspring following paternal transmission.

Pregnant guinea pigs were treated with 3 courses of either saline (Veh) or sGC (betamethasone) in late gestation, and then delivered undisturbed (term ~69 days). Adult F1 male offspring were mated with naïve females to produce F2 offspring. Male and female F2 offspring underwent behavioural and HPA testing from days 19-35. On days 19 and 24 (pre- and post-weaning), offspring were tested in an open field (OF) for locomotor activity and anxiety (thigmotaxis); saliva was collected to assess HPA function. On day 23, offspring were tested in an acoustic startle chamber for prepulse inhibition (PPI; attention) and startle (anxiety). On day 35, radiotelemetry was used to assess 24-hour locomotor activity in the home cage.

There were no effects of sGC on locomotor activity in the OF or home cage. Over the first 5 minutes of the OF on day 19, thigmotaxis was increased in sGC female offspring, but reduced in sGC male offspring ($P<0.05$). In F2 female offspring, sGC resulted in a greater HPA response to stress on day 19 ($P<0.05$), and a trend towards increased response on day 24 ($P=0.07$). There were no effects of sGC on HPA response to stress in male offspring. sGC resulted in reduced PPI in F2 juvenile female offspring ($P<0.05$), but did not affect PPI in males. There were no effects of sGC on acoustic startle response in F2 offspring.

Prenatal treatment with sGC resulted in paternal transmission of reduced attention, increased anxiety and increased HPA response to stress in young female but not male offspring. Contrary to our previous study of maternal transmission, there does not appear to be paternal transmission of the effects of sGC on locomotor activity. The effects on attention, anxiety and HPA function are most pronounced in females, which may suggest sex-specific programming across generations. Alterations in stress-related behaviour and HPA function early in life are associated with long-term neurologic and cardiometabolic health issues. Therefore, it is necessary to determine whether the effects observed in young second generation animals persist into adulthood, and to identify the mechanisms by which these effects occur.

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Reference(s):

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Keywords: Experimental Models, Prenatal, Transgenerational

Presented in Session: Plenary IV: Developmental exposures and neurobehavioral disorders
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Developmental stress and children's telomere length

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Introduction: Chronic stress is frequently invoked as an explanation for the adverse effect of harsh environments. Accelerated telomere shortening tracks lifetime exposure to stress and may be a useful biomarker. Work from many laboratories reveals that gene variants in dopaminergic or serotonergic pathways moderate the association between the social environment and children's health and wellbeing, reviewed in (1). We used data from The Fragile Families and Child Well Being Study (FFCWS—www.fragilefamilies.princeton.edu), to examine the relationship between social disadvantage, genotype, family instability, and TL. The FFCWS follows a stratified, multi-stage, probability sample of 4500 children (and their mothers) born in large U.S. cities (200,000+) between September 1998 and September 2000, with an oversample of children born to unmarried parents (three-quarters unmarried, one-quarter married). Saliva DNA was collected at age 9 years. In a subset of 40 subjects, African-American boys who grew up in highly disadvantaged environments had shorter telomeres (age 9) than boys who grew up in highly advantaged environments. We also found that the association between the social environment and TL is moderated by genetic variation within the serotonin pathways (2). Over the full DNA sample of 5600, the average TL for our children was 7.9 Kb and for mothers was 6.8 Kb. Genotypes for HTTLPR, and STin2 were obtained by PCR followed by electrophoresis;TPH2 was determined by RT-PCR(2).

Results: The results of the initial study with 40 boys showed that living in disadvantaged environments was associated with a 19% shorter TL (p=0.02). Having a mother with a high school degree was associated with a 32% increase in child's TL (p=0.006). Being exposed to multiple changes in family structure was associated with a 40 percent decline in boys' TL (p=0.010). There was a significant interaction between the social environmental and serotonin pathway genotypes(2). In a current analysis of TL in all 5600 DNA samples, maternal TL correlated with age: (~40 bp/year). Firstborn children had significantly shorter telomeres, and similar to our previous result, TL and income were directly and significantly correlated. Child TL was adversely affected by the departure of a biological father. Taking into account the average rate of telomere shortening, the death of the biological father is equivalent to about 9 years of "telomere age" and having the biological father incarcerated to approximately 3-3.5 years "lost" for the mother.

Conclusion: This research confirms the tight linkage between social environment, family stability, and telomere shortening. In particular, perturbations in father participation in the family appear to have a major effect on child stress as measured by the TL. Our findings also suggest that an individual's genetic architecture affects the magnitude and direction of the physiological response to exogenous stressors.

Source(s) of support: Funding was provided by the NICHD (R01HD076592, R01HD36916, R01HD39135, and R01HD40421), and others.

Reference(s):

1. Mitchell, C., et al (2013). American Journal of Public Health, 103 Suppl 1, S102-110.
2. Mitchell, C., et al(2014), Proc Natl Acad Sci USA, 111(16), 5944-5949

Abstract type: Population Research
Category: Nervous System
Keywords: Birth Cohort, Epidemiology, Mechanisms & Pathways

Presented in Session: Breakout 7: Emerging concepts, new endpoints and methodologies
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Identification of epigenetic patterns in birth cohorts

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Epigenetic marks such as DNA methylation and microRNA are altered by environmental exposures and are thus exciting prospects as biomarkers of early life environments. Their persistence and impact on gene expression makes them potential predictors of health impacts. High-throughput platforms utilizing microarrays and next generation sequencing approaches enable the measurement of a growing number of epigenomic marks with tradeoffs for coverage, cost, and precision.

The standardization of these assays (many offered as commercial services) enables epigenomic approaches in larger cohorts. It also shifts the burden away from laboratory procedures towards the computational challenges of understanding, processing, learning from and communicating the complex relations captured within epigenomic datasets.

The increasing coverage of epigenomic platforms, measuring hundreds to millions of epigenetic marks, creates new opportunities and challenges in epigenetic epidemiology. The promise of epigenome-wide studies is the potential for discovering new biomarkers in relevant and yet undiscovered biologic pathways. However, the increasing breadth of coverage can become a curse of dimensionality when corrections for multiple comparisons penalize these extremely wide datasets in which the number of marks far exceeds the number of samples. This new challenge can be addressed in three main ways; 1) improved measurements, 2) improved analytic approaches, and 3) larger sample sizes through meta-analysis. We will present recent examples and prospects for all three efforts as well as some promising new developments in computational and statistical approaches to identifying epigenomic biomarkers in environmental epidemiology.

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Reference(s):

Abstract type: Population Research
Category: Other: Epigenetics
Keywords: Epidemiology, Epigenetics, Prenatal

Presented in Session: Breakout 7: Emerging concepts, new endpoints and methodologies
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Arsenic exposure, breast feeding and infant microbiome composition in a US birth cohort

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Emerging evidence suggests that the composition of the infant intestinal microbiome may play important roles in mediating protection from a range of health outcomes in early childhood and later in life including allergy and asthma, obesity, and infection. The specific prenatal and early life exposures that influence the development of the intestinal microbiome in healthy infants remain largely unexplored. Limited evidence points to exposure to infant formula (vs. human milk) as one potentially critical factor in microbiome composition in infancy. In vitro and animal experiments also point to a complex relationship between the intestinal microbiota and arsenic exposure pre- and postnatally. We aimed to evaluate the relationships between these two potentially critical factors and the composition of the infant intestinal microbiome in a large US cohort of healthy infants and their mothers. We characterized the infant intestinal microbiome using high throughput sequencing targeting the V4-V5 region of microbial 16s rDNA in 150 infant stool samples followed as part of New Hampshire Birth Cohort Study. We classified bacterial sequencing reads at the genus level and examined correlations between the relative abundance of each genus and either feeding method (exclusive breast feeding, exclusive formula feeding, or combination feeding) or total maternal urinary arsenic levels during pregancy using generalized linear models. We also used unsupervised and supervised classification methods to examine relationships between microbiome community composition, feeding, and maternal urinary arsenic levels. Across all samples, we observed a diverse intestinal microbiome that increased in diversity with the age of the infant at the time of sampling. We found that both feeding method and maternal urinary arsenic were associated with differential relative abundance of a number of microbial genera. Infants born to mothers with relatively high maternal urinary arsenic levels during pregnancy, indicating significant prenatal arsenic exposure, harbored distinct microbial communities compared with infants born to mothers with limited arsenic exposure during pregnancy. Infants who were fed exclusively human milk had intestinal microbiomes that were distinct from those fed exclusively formula. In addition, the microbiome profiles of infants who were fed both human milk and formula were more similar to those of infants fed only formula than they were to infants fed only human milk. We conclude that the composition of the infant microbiome in early life may be influenced by feeding practices as well as by prenatal exposure to toxic metals such as arsenic. Detailed, longitudinal evaluations of the relationships between the intestinal microbiome composition and common prenatal and postnatal infant exposures will provide a needed foundation for understanding the potential role of the microbiome in mediating the influence of these exposures on disease risk in children.

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Category: Other: Microbiome
Keywords: Birth Cohort, Exposure Assessment, Prenatal

Presented in Session: Breakout 7: Emerging concepts, new endpoints and methodologies
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Potential impact of pesticide exposures during pregnancy on the newborn's metabolome

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The use of pesticides can lead to human exposure to numerous molecules especially in the vicinity of agricultural applications. Our preliminary study showed modifications of urinary metabolites potentially involved in oxidative stress and energy metabolism in pregnant women living in towns where a large part of the surface area was devoted to cereal crops. In early-life, such exposures and related metabolic changes in women may be responsible for adverse developmental effects. However, human health risks associated with exposure to complex mixtures are currently under-explored.

This project aims at answering the following questions: what is the influence of exposures of pregnant women to multiple pesticides on the metabolome of the newborn? What mechanistic pathways could be involved in the metabolic changes observed?

Based on the PELAGIE cohort (Brittany, France), 131 pregnant women who gave birth to a boy and provided a cord-blood sample, were classified into 3 groups according to the surface of land dedicated to cereal crops in their town of residence. Nuclear magnetic resonance-based metabolomics analyses were performed on plasma samples. The orthogonal signal correction (OSC) algorithm was used to remove confounding variability. Partial Least Squares Regression-Discriminant Analysis (PLS-DA) was applied to filtered data to discriminate blood metabolic profiles according to the 3 exposure groups. For the most discriminant metabolites (variable importance in the projection > 1), polytomous regressions were used to additionally adjust for potential individual confounders. The PLS-DA model has correctly discriminated the cord-blood metabolic profiles according to the 3 groups of exposure. Unit variance scaling was applied on filtered data and results were expressed as R2=76.1% and Q2=0.596. After controlling for maternal age, parity, body mass index, smoking habits and gestational age at birth, statistically significant increases were observed for dimethylamine, aceto-acetate, citrate, alanine, lactate, citrate, dimethylamine, methylhistidine. An increasing trend was also identified for lipids. Statistically significant decreases were observed for creatinine, creatine, acetate, glutamate, lysine, isoleucine, serine, tyrosine, suggesting an impact on the energetic metabolism and amino-acids metabolism in cord blood of male infants. These metabolic changes observed in newborn's blood associated with the pesticide exposure groups of their mothers may be related to the metabolic changes previously observed on the prenatal urine samples of the mothers. This suggests a potential role of complex environmental pesticide mixture exposures on the oxidative stress imbalance.

Source(s) of support:

Reference(s):

Abstract type: Basic Research
Category: Other: oxidativ stress
Keywords: Birth Cohort, Epidemiology, Mechanisms & Pathways

Presented in Session: Breakout 7: Emerging concepts, new endpoints and methodologies
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Stem cells as targets that lead to increased cancer susceptibility

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Esther Calderon, University of Illinois at Chicago, IL, US
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While early-life estrogens play a physiological role in normal prostate gland development and function, inappropriate estrogenic exposures, either in timing, dose or type, can reprogram the gland and increase its susceptibility to hormonal carcinogenesis with aging. Previous research using rodent models identified prostate stem cell disturbances following developmental estrogenization, thus we hypothesize that estrogen imprinting of the prostate occurs, in part, through stem and progenitor cell reprogramming that permits long-term memory of this exposure throughout life. To test this directly and address whether humans are similarly susceptible, we developed in vitro and in vivo models utilizing primary prostate cells from organ donors as well as human embryonic stem cells (hESC). Stem and progenitor cells were isolated from primary prostate epithelial cells (PrEC) of young, disease-free organ donors using FACS and 3-D prostasphere (PS) culture. Studies confirmed both cell populations as ERα+ and ERβ+ and showed that estradiol-17□ (E2) significantly increased their proliferation and maintained stemness. The estrogenic endocrine disruptor, bisphenol A (BPA), likewise increased stem-progenitor cell self-renewal and stem-related gene expression. While E2 induced genomic ERE signaling, both E2 and BPA initiated equimolar activation of membrane ERs with equivalent, rapid induction of p-Akt and p-Erk which provides a mechanistic framework for robust BPA actions. Further, findings identify reprogrammed genes and sncRNAs in prostate progenitor cells with E□ and BPA exposure indicating epigenetic reprogramming. An in vivo model to assess carcinogenicity was developed using human PS cells mixed with rat UGM and grown as renal grafts in nude mice, forming prostate structures with normal, PSA+ human prostate epithelium at 1 month. Exposure to E2+T for 2-4 months led to PIN or PCa at low incidence (13%). Developmental BPA exposure was modeled by daily feeding of hosts for 2 wk after grafting (0.39-1.35 ng free-BPA/ml serum). Upon E2+T for 2-4 mo, the PIN/PCa incidence increased ($P<0.01$) to 33-36% and further increased to 46% ($P<0.01$) when PS cells were additionally exposed to BPA in vitro. We also generated a pioneer in vitro model of directed differentiation of hESC into prostatic organoids. Exposure to 1-10 nM BPA resulted in focal clusters of stem cells within the organoids, a phenotype not observed in controls, which suggests aberrant stem-cell self-renewal. Together these findings clearly demonstrate that human embryonic and adult prostate stem and progenitor cells are direct targets of E2 and BPA which drive stem cell self-renewal. Further, developmental BPA exposure reprograms the human prostate epithelium, leading to heightened sensitivity to a secondary rise in estrogen, as occurs in aging men, with a resultant increase in PCa incidence. We thus propose that humans are susceptible to developmental estrogen/EDC imprinted prostate disease with aging.

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Reference(s):

Abstract type: Basic Research
Category: Cancer
Keywords: Experimental Models, Mechanisms & Pathways, Stem cells

Presented in Session: Breakout 8: Early life antecedents of cancer
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Progesterone and overlooked endocrine pathways in breast cancer pathogenesis

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Exposure to reproductive hormones affects breast cancer risk and promotes disease progression. In particular, the number of menstrual cycles a woman experiences during her life time correlates with breast cancer risk. We combine mouse genetics with tissue recombination techniques to study hormone action in vivo and provide evidence that progesterone is a major regulator of cell proliferation and stem cell activation in the adult mammary gland. Two progesterone receptor (PR) targets, Receptor activator of Nf□B ligand (RANKL), and Wnt4 have distinct roles as downstream mediators of PR signaling.

Perinatal exposure to environmentally relevant doses of bisphenol A (BPA) alters mammary gland development. In the adult mammary gland, mammary epithelial cell numbers are increased and induction of RANKL and Wnt4 transcripts in response to progesterone is increased. A model of how BPA may increase suceptibility to breast cancer is presented.

Source(s) of support:
Reference(s):

Abstract type: Basic Research
Category: Cancer
Keywords: Experimental Models, Mechanisms & Pathways, Perinatal

Presented in Session: Breakout 8: Early life antecedents of cancer
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Prenatal and lifespan exposure enhances the sensitivity of carcinogenicity bioassays: The cases of artificial sweeteners aspartame and sucralose

Michela Padovani, Cesare Maltoni Cancer Research Center, Ramazzini Institute, Italy; Morando Soffritti, Cesare Maltoni Cancer Research Center, Ramazzini Institute, Italy

Carcinogenicity bioassays in rodents have long been recognized and accepted as a valuable and important predictor of potential cancer in humans. As recommended by regulatory agencies, most carcinogenicity assays tend to have a duration of 2 years, starting at 6-8 weeks of age and ending at 110 weeks, a period which represents only 2/3 of the animals' lifespan. Conducting bioassays on large groups of animals exposed from fetal life until natural death increases the sensitivity of studies and their potential to detect and assess risk, as shown by the cases of the largely used artificial sweeteners aspartame and sucralose. Aspartame (APM) is present in more than 6,000 products, including over 500 medicines. Principal consumers include children and women of childbearing age. Carcinogenicity bioassays performed by producers of APM on rats and mice in the early '70s, and later on transgenic mice by the US NTP, failed to show any carcinogenic effects. A recent epidemiology study showed an increased risk of non-Hodgkin's lymphoma and multiple myeloma in men who consumed diet soda sweetened with APM. Sucralose is an organochlorine disaccharide manufactured from sucrose by substituting chlorine for 3 of its -OH groups. Oral intake of sucralose is largely absorbed and excreted unchanged. It is not genotoxic and it has been shown to be non-carcinogenic in conventional long-term rodent bioassays.

Despite reassurances by regulatory agencies, health-related concerns regarding the safety of APM and sucralose persist. The Ramazzini Institute has undertaken a large project encompassing several experiments on rodents in which: 1) APM was administered in feed at various doses to a large number of rats and mice per group per sex, starting treatment at different ages (including prenatally) until natural death and 2) sucralose was administered to large group of mice from fetal life until death. APM, administered from 8 weeks of age for the lifespan to Sprague-Dawley rats, induced a significant increased incidence of lymphomas/leukemias, of neoplastic lesions of the renal pelvis and ureter in females, and malignant schwannomas of the peripheral nerves in males. In a second experiment in which rats were exposed from prenatal life until death, the carcinogenic effects increased, demonstrating a higher incidence of lymphomas/leukemias in males and females, and of mammary cancer in females. A third study on Swiss mice, exposed to APM from prenatal life until death, showed a significant increased incidence of hepatocellular and alveolar/bronchiolar carcinomas in males.

Concurrently with the APM mice study, a prenatal carcinogenicity study of sucralose on mice was performed. Unpublished results of the carcinogenic effects of sucralose will be presented.

Overall, the results of these studies on large groups of animals, exposed from fetal life and then for lifespan, show how this approach is more sensitive than conventional bioassays approved by regulatory agencies.

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Reference(s):

Abstract type: Basic Research
Category: Cancer
Keywords: Experimental Models, Prenatal, Public Health

Presented in Session: Breakout 8: Early life antecedents of cancer
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Prenatal exposure of mice to the human liver carcinogen Aflatoxin B1 reveals a critical window of susceptibility to genetic change

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It has become axiomatic that critical windows of susceptibility to genotoxins exist and that genetic damage in utero may be a trigger for later life cancers. Data supporting this critical window hypothesis are remarkably few. This study provides a quantitative bridge between DNA damage by the liver carcinogen aflatoxin B1 (AFB1) during prenatal development and the risk of later life genetic disease. AFB1 was given to pregnant C57BL/6J mice, carrying F1 gestation day 14 (GD14) embryos of the B6C3F1 genotype. Ultra-high performance liquid chromatography and mass spectrometry (UPLC-MS) using aflatoxin-15N5-guanine adduct standards afforded measurement of the AFB1-N7-Gua and AFB1-FAPY adducts six hours post dosing in liver DNA of mothers and embryos. A parallel cohort gave birth and the livers of the F1 were analyzed for mutations in the gpt gene at three and ten weeks of age. The data revealed mutational spectra dominated by G:C to T:A mutations in both the mother and offspring that are characteristic of AFB1 and distinct from background. It was shown that adducts in GD14 embryos were 20-fold more potent inducers of mutagenesis than adducts in parallel-dosed adults. This sensitivity enhancement correlated with Ki67 staining of the liver, reflecting the proliferative potential of the tissue. Taken together, these data provide insight into the relative genetic risks of prenatal and adult exposures to AFB1. Early life exposure, especially during the embryonic period, is strikingly more mutagenic than treatment later in life. Moreover the data provide a baseline against which risk prevention strategies can be evaluated.

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Reference(s):

Abstract type: Basic Research
Category: Cancer
Keywords: Experimental Models, Prenatal, Other: Genetic mutation and Cancer

Presented in Session: Breakout 8: Early life antecedents of cancer
Date/Times: Tuesday, October 28, 3:30-5:00 PM

Transgenerational effects on cardiac development in zebra fish

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Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD) is the prototype Dioxin-Like Chemical (DLC) and an aryl hydrocarbon receptor (AHR) agonist. DLCs are significant global contaminants. Dioxin exposure is associated with toxicity in many organ systems in humans and other vertebrates. While the acute developmental effects of dioxin exposure have been extensively studied, the long-term consequences of early sublethal exposure are poorly understood. This is difficult to study in humans for a number of reasons, including long life span, individual genetic differences, and diverse exposures to different chemicals and life styles. We have chosen zebrafish (Danio rerio) as a model to study adult and transgenerational effects of sublethal dioxin exposure during development. We find that this is a superb model system that is already yielding information about how early low-level exposure produces later effects in the adult and in subsequent, unexposed generations. We find that early sublethal (1 h @ 50 pg/ml in water) exposure produces toxicity later in adulthood. We find adult toxicity in heart, brain, reproductive systems, and skeleton. To date, we know that the effects on reproduction and skeletal formation occur transgenerationally in the F1 and unexposed F2 generations, and suspect that other as yet undiscovered effects may be found in subsequent generations as well. It is important to determine how many generations these effects will persist through. We propose that the zebrafish is a cost-effective model system for evaluating the transgenerational effects of toxic chemicals and their role in the fetal basis of adult disease.

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Reference(s):

Abstract type: Basic Research
Category: Reproductive System
Keywords: Experimental Models, Transgenerational, Fetal basis of adult disease

Presented in Session: Plenary V: Early-life stresses and late-life disease
Date/Times: Wednesday, October 29, 8:30-10:00 AM

Developmental origins of cardiovascular disease

Johan Eriksson, MD, DMSc., University of Helsinki, Finland

Slow and non-optimal prenatal growth has repeatedly been associated with several adverse health outcomes and non-communicable diseases (NCDs) including cardiovascular disease and type 2 diabetes in adult life.

However, these long-term affects of prenatal growth are largely modified by growth in childhood. When the intrauterine "milieu" is sparse it can program the fetus metabolically to adapt to conditions characterized by nutritional shortage. This could be the consequence of maternal malnutrition, placental dysfunction as well as other causes leading to disturbances in the nutritional supply line from mother to fetus. However, when an infant programmed to live in sparse conditions encounters a surrounding rich in energy supply this usually has a negative influence on degree of adiposity and body composition. Consequently, the risk for cardiovascular disease and type 2 diabetes will increase. The term "mismatch" has been used to describe the described situation.

Within the Helsinki Birth Cohort Study (HBCS), 13 345 people born 1934-44 have been followed longitudinally. HBCS is one of the few birth cohorts worldwide with life course data available from prenatal life to late adulthood. A small body size at birth is a risk factor for cardiovascular disease in adult life. However the mismatch between a small body size at birth and higher body mass index in later childhood is a major factor influencing later risk for cardiovascular disease. Those being born thin had in general the highest risk for coronary heart disease. However this increased risk associated with thinness at birth was markedly modified by growth in childhood. Being born thin but belonging to the highest BMI group at age 11 years was associated with a more than four-fold risk for cardiovascular disease. In other words the "journey" from being born thin to higher adiposity is of greater importance than the body size attained per se. Similar associations have been described in relation to type 2 diabetes.

The underlying mechanisms explaining these associations could be programming on body composition, metabolism in general and more specifically hepatic lipid metabolism. This is supported by postprandial studies showing that a slow growth during infancy is associated with a more atherogenic lipid profile. Also genetic and epigenetic mechanisms need to be considered. The concept of early metabolic programming is still valid in today's world. The recognition of pathways of growth associated with health adversities is of major importance from a preventive point of view.

Source(s) of support:

Reference(s):

Abstract type: Clinical Research
Category: Cardiovascular System
Keywords: Birth Cohort, Prenatal, Postnatal

Presented in Session: Plenary V: Early-life stresses and late-life disease
Date/Times: Wednesday, October 29, 8:30-10:00 AM

Early-life stresses and schizophrenia risk

Ezra S. Susser, MD, DrPH, Columbia University, US

Evidence has been accumulating that early-life stresses are associated with increased risk of schizophrenia among offspring. A wide range of "stresses" have been studied, including nutritional deficiencies, infections, toxins, maternal bereavement, and migration during the prenatal and/or early postnatal period. Mechanisms have been hypothesized, but not established, for these exposures. This paper will first provide a brief overview of this field. Then, it will focus on nutrition, infection, and toxins, the latter two very succinctly. It will present data supporting the associations, discuss mechanisms that have been proposed and/or studied, and suggest future directions.

Source(s) of support:

Reference(s):

Abstract type: Population Research
Category: Nervous System
Keywords: Birth Cohort, Epidemiology, Prenatal

Presented in Session: Plenary V: Early-life stresses and late-life disease
Date/Times: Wednesday, October 29, 8:30-10:00 AM

Prenatal and childhood adversity and inflammation in adulthood

Natalie Slopen, University of Maryland College Park, US; Eric Loucks, PhD, Brown University, US; Allison A Appleton, ScD, University of Albany, School of Public Health, US; Ichiro Kawachi, PhD, Harvard School of Public Health, US; Laura D Kubzansky, Harvard School of Public Health, US; Amy L Non, PhD, Vanderbilt University, US; Stephen L Buka, ScD, Brown University, US; Stephen E Gilman, ScD, , Harvard School of Public Health, US

Background: Children exposed to social adversity carry a greater risk of poor physical and mental health into adulthood. This increased risk is thought to be due, in part, to inflammatory processes associated with early adversity that contribute to the etiology of many adult illnesses. The current study asks whether aspects of the prenatal social environment are associated with levels of inflammation in adulthood, and whether childhood adversity may contribute independent of prenatal measures. Methods: We examined associations of prenatal and childhood adversity assessed through direct interviews of participants in the Collaborative Perinatal Project between 1959-1974 with blood levels of C-reactive protein in 355 offspring interviewed in adulthood (mean age=42.2 years). Linear and quantile regression models were used to estimate the effects of prenatal adversity and childhood adversity on adult inflammation, adjusting for individual characteristics of age, sex, and race and potential confounders.

Results: In separate linear regression models, high levels of prenatal and childhood adversity were associated with higher CRP in adulthood. When prenatal and childhood adversity were analyzed together, our results support the presence of an effect of prenatal adversity on (log) CRP level in adulthood (β=0.73, 95% CI: 0.26, 1.20) that is independent of childhood adversity and potential confounding factors including maternal health conditions reported during pregnancy. Supplemental analyses revealed similar findings using quantile regression models and logistic regression models that used a clinically-relevant CRP threshold (>3 mg/L). In a fully-adjusted model that included childhood adversity, high prenatal adversity was associated with a 3-fold elevated odds (95% CI: 1.15, 8.02) of having a CRP level in adulthood that indicates high risk of cardiovascular disease.

Conclusions: Social adversity during the prenatal period is a risk factor for elevated inflammation in adulthood independent of adversities during childhood. This evidence is consistent with studies demonstrating that adverse exposures in the maternal environment during gestation have lasting effects on development of the immune system. These results suggest that interventions to improve the social and environmental conditions of pregnancy could promote health over the life course. It remains necessary, though, to identify the mechanisms that link maternal conditions during pregnancy to the development of fetal immune and other systems involved in adaptation to environmental stressors.

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Reference(s):

Abstract type: Population Research
Category: Immune System
Keywords: Birth Cohort, Prenatal, Public Health

Presented in Session: Plenary V: Early-life stresses and late-life disease
Date/Times: Wednesday, October 29, 8:30-10:00 AM

Role of environmental chemical exposures

Linda S. Birnbaum, PhD, DABT, ATS, National Institute of Environmental Health Sciences/NIH and National Toxicology Program, US

Evidence emerged in the early 1990s suggesting that low-dose chemical exposures in the absence of overt teratogenic effects at birth could, ultimately, result in later dysfunction and disease. These observations were consistent with the Developmental Origins of Health and Disease (DOHaD) concept that shifted the emphasis of developmental toxicology research from the study of mutagens and birth defects to altered developmental programming resulting in organizational changes during development. In the two decades since, environmental health scientists have focused increasing effort on identifying the mechanisms by which low levels of toxicants may impact organisms during sensitive developmental windows. Because development is precisely controlled by growth factors and hormones, endocrine disrupting chemicals (EDCs) are of particular concern. Experimental models and increasingly supportive evidence from human studies have shown EDCs to alter developmental programming and establish clear associations with increased incidence and susceptibility to disease later in life. The list of chemicals that can cause altered developmental programming as well as the list of diseases shown to be affected by environmental exposures continues to expand. Indeed, non-communicable diseases like obesity, diabetes, cardiovascular and respiratory, behavior and neurological disorders, male and female reproduction, and cancer can all be linked to developmental exposures to environmental chemicals. Recent animal data showing intergenerational and transgenerational effects from developmental exposures has added a new element of concern that will require additional research to identify the long-term impacts. The scientific community continues to elucidate the various mechanisms by which environmental exposures lead to increased risk of disease, the mechanisms behind the long latency and multigenerational effects, as well as the development of biomarkers of exposure and disease susceptibility which can be used to aid in disease prevention and intervention.

Source(s) of support:

Reference(s):

Abstract type: Population Research
Category: Other: Environmental chemical exposure
Keywords: Public Health

Presented in Session: Plenary VI: Developing a global definition of DOHaD
Date/Times: Wednesday, October 29, 10:30 AM - 12:00 PM

Role of nutrition

Matthew W. Gillman, MD, Harvard Medical School, US

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Date/Times: Wednesday, October 29, 10:30 AM - 12:00 PM

Role of stress

Deborah Cory-Slechta, PhD, University of Rochester Medical School, US

Stress is an inevitable component of human life, and under some conditions can lead to subsequent disease and pathologies. Stress is mediated by glucocorticoids, and glucocorticoid receptors are found in almost all cells, explaining why stress has such multi-targeted effects. Glucocorticoids, released from the HPA (hypothalamic pituitary adrenal) axis in response to stress, are essential for metabolism, immune regulation, normal development, brain function and cognition and subsequent stress responsivity. Prenatal or maternal stress in particular has been considered to produce protracted adverse consequences, often sex-dependent, for multiple organs and systems, including the brain, through its programming effects. Indeed, overexposure to glucocorticoids is considered one mechanism of fetal programming through transcriptional and non-genomic actions of glucocorticoids. Increased maternal glucocorticoid levels can overcome placental/fetal barriers and elevate fetal glucocorticoid levels. Consequences for fetal brain structure include altered neurotransmitter function and synaptic plasticity and alterations in behavior, cognition and risk for neuropsychiatric disorders in adulthood. Because stress effects are mediated via the HPA axis and its interactions with brain mesocorticolimbic circuitry (prefrontal cortex, nucleus accumbens, hippocampus), it has the potential to synergize with neurotoxicants that share these substrates, such as the neurotoxic metals lead and methylmercury. Like prenatal stress, both lead and methylmercury can alter corticosterone levels, and induce behavioral effects mediated by mesocorticolimbic brain circuitry, suggesting that combined exposures could lead to enhanced neurotoxicity. As prenatal stress and neurotoxic metal exposures can be co-occurring risk factors in many populations, the potential for enhanced toxicity has significant public health protection consequences. In a series of experimental studies, we have demonstrated such enhanced neurotoxicity, including situations where effects of lead or methylmercury are only evident in combination with prenatal stress, i.e., an unmasking phenomenon. These include adverse behavioral effects as well as altered HPA axis function. In some cases, the concentration-effect functions for neurochemical changes produced by either lead or methylmercury can be dramatically different in animals also subjected to prenatal stress than those not so treated. Important to advancement of this field is the recognition that maternal stressors currently used in animal studies each can produce different profiles of physiological consequences, and, further, may not adequately capture the types of prenatal stress that characterize the human conditions that they are intended to mimic. Furthermore, given that the third trimester human equivalent occurs during early postnatal life in rodents, combined exposures to prenatal and early postnatal stress may best simulate human prenatal stress.

Source(s) of support: NIH P30 ES001247; EPA RD 83457801; R01 ES012712

Reference(s):

(1) Weston HI et al., Neurotoxicology 2014; Jul 7;44C:169. (2) Weston HI et al., Neurotoxicology 2014; 41:123. (3) Cory-Slechta, DA et al., Toxicological Sciences, 2010; 117:427.

Abstract type: Translational Research
Category: Nervous System
Keywords: Epidemiology, Experimental Models, Prenatal

Presented in Session: Plenary VI: Developing a global definition of DOHaD
Date/Times: Wednesday, October 29, 10:30 AM - 12:00 PM

Integration of "environment" into DOHaD definition

Jerrold J. Heindel, PhD, National Institute of Environmental Health Sciences/NIH, US

The original Developmental Origins of Health and Disease (DOHaD) hypothesis was based on the principle that undernutrtion during gestation, that resulted in low birth weight, predisposes adults to cardiac and metabolic disorders due to fetal programming that permanently shaped the body's structure, function and metabolism. Later it was determined that birth weight is a proxy for fetal nutrition and endocrine environment such that in utero nutrition can be associated with elevated disease risk regardless of weights at birth and early childhood. It is now clear that stress or exposure to environmental chemicals during development, mainly chemicals with endocrine disrupting activity (EDCs), can also lead to a fetus with subtle functional changes in specific tissues that can lead to increased susceptibility to disease/dysfunction later in life. While developmental programming due to stress can also lead to increased disease susceptibility, the majority of the current data focuses on the two fields of nutritional and environmental chemical effects during development. They can be considered two sides of the same coin with many common aspects. Either nutritional imbalance or environmental chemical exposures:

- Cause subtle functional changes difficult to detect without 'omics approaches and assessment at appropriate stages across the lifespan.
- Exert tissue specific effects when tissues are developing (in utero and/or the first years of life).
- Result in latency between "exposure" and disease/dysfunction.
- Result in sex specific effects.
- Result in susceptibility to many of the same non-communicable diseases.
- Result in effects that can be transmitted via the germ line to future generations.
- Likely act at least in part via similar mechanisms that result in alterations in epigenetic marks that result in altered developmental programming.

The fact that both under or over nutrition and environmental chemical exposures have so much in common and in fact likely occur together to result in increased susceptibility to many of the same disease/dysfunctions make it imperative that both fields work together to get a real picture of the effect of altered developmental programming and disease outcomes across the lifespan. An important step in achieving this goal is for both fields to use common terminology, and to agree that the term DOHaD refers to both altered nutrition and/or exposures to environmental contaminants.

Source(s) of support:

Reference(s):

Abstract type: Translational Research
Category: Other: DOHaD
Keywords: Experimental Models, Mechanisms & Pathways, Prenatal

Presented in Session: Plenary VI: Developing a global definition of DOHaD
Date/Times: Wednesday, October 29, 10:30 AM - 12:00 PM

The precautionary principle in action: European approaches to environmental risk governance

Hans Bruyninckx, PhD, European Environment Agency, Denmark

The precautionary principle in action: The European Environment Agency (www.eeaa.europa.eu) is a European Union body that provides knowledge in support of EU environment policies along three timelines (2015-2020, 2030 and 2050).

As part of its mandate, the EEA has been informing decision-making under conditions of uncertainty through applying the precautionary principle (PP): two reports published in 2001 and 2013 under the chapeau "Late Lessons from Early Warnings" inform the knowledge base of this work.

The relevance to PPTOX is illustrated by several case studies in the Late Lessons reports, including DES, PCBs, BPA, , lead and mercury. These case studies and others offer several broad insights: for example, the costs of action are always exaggerated and the harm of pollution is always worse than originally feared.

While these reports largely reviewed the past, they also offer insights on how the PP and other policy tools can help to prevent similar errors occurring in future. This is important for Europe and many other regions of the world that are confronted by systemic risks that cannot be solved by prevailing governance approaches. Long-term transitions are required in the socio-technical systems that fulfil society's needs through profound changes in dominant structures, thinking and practices.

Risk governance is a central challenge, as the impact of future changes will be inherently highly uncertain. Building more appropriate risk governance mechanisms will require reflection, inter-alia, on the role of environmental regulations, market instruments and science in support of transitions. False positive and false negatives may both occur. The PPTOX paradigm is a reminder that risk governance must be based on responsible consideration of existing knowledge, the associated uncertainties and their implications.

Source(s) of support:

Reference(s):

Abstract type: Basic Research
Category: Other: European approaches to environmental risk governance
Keywords: Exposure Assessment, Public Health, Regulatory Issues

Presented in Session: Plenary VII: Translating science to improve public health
Date/Times: Wednesday, October 29, 1:30-3:00 PM

The clinician's role in protecting early development

Jeanne A. Conry, MD, PhD, The Permanente Medical Group, US

Not provided.

Source(s) of support:
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Abstract type: Clinical Research
Category: Other: Clinician's role
Keywords:

Presented in Session: Plenary VII: Translating science to improve public health
Date/Times: Wednesday, October 29, 1:30-3:00 PM

Translating ecological effects to protection of human health

Louis J. Guillette, PhD, Medicial University of South Carolina, US

Wildlife, domesticated and laboratory animals have been used to predict detrimental human health effects from environmental variables for decades. There is growing concern, however, that exposure to low levels of 'endocrine-active' contaminants early in embryonic development coupled with altered climate can lead to altered phenotypes, and disease. Although each species is unique, molecular, cellular and physiological systems are conserved allowing insight into the process of human health from 'sentinel species' studies. A large and growing literature has now demonstrated that 1) classical gene mutations likely account for less than 20% of known disease (in many cases as low at 8 – 10 %), 2) linear dose response curves poorly predict adverse responses to low levels of environmental contamination and exposure to complex mixtures, and 3) altered gene expression, via epigenetic mechanisms, can be induced by varying diets, stress and low level exposure to various environmental contaminants, including metals and organics. These epigenetic modifications are being readily linked to predisposition for disease. This talk reviews, in part, the work done by my laboratory on wildlife species, such as the American alligator, examining the effects of various environmental contaminants on the development and functioning of the endocrine and reproductive systems from the genetic to organismal level. I will relate this work to implications for modern human health care as well as environmental management and conservation.

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Reference(s):

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Category: Reproductive System
Keywords: Epigenetics, Experimental Models, Mechanisms & Pathways

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Date/Times: Wednesday, October 29, 1:30-3:00 PM

Incorporation of principles from research on early life exposure and effects into analysis for environmental health policies: Case studies from the US

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Research from a variety of fields has expanded understanding of the significance of early life exposure, including prenatal and even preconception exposure, to environmental agents and to the influence of other stressors. This study looked at the extent to which analyses used to characterize and assess environmental exposures and their health significance incorporated key findings from this research. The first step in the project was to identify principles emerging from the research that could be incorporated into policy-relevant assessments. The second step was to select case studies to analyze to determine the extent to which this had occurred and to understand the rationale provided for doing so (or not doing so). The case studies selected were related to the assessment of the residual risk remaining after implementation of technology based controls for hazardous air pollutants within specific sectors including refineries, smelters, and other industrial processes. Such reviews are intended to specifically examine health related concerns using a scientific approach. However, the scientific review has become defined in part by findings from litigation that originate from judicial rather than scientific conclusions. The results found that the analysis have evolved in recent years to better take into account the importance of highly exposed and more susceptible populations and to recognize a wider array of health concerns than had been true in earlier reviews. However, the analyses cling to methods for risk assessment that, while perhaps widely accepted, are no longer consistent with emerging scientific knowledge. These results suggest that targeted translation directed toward unpacking and analyzing principles derived from legal decisions is necessary to contribute to uptake of new research regarding early life exposures and effects. This may be a new direction for work for research translation in environmental health.

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DOHaD Society efforts to build a global DOHaD network

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The International DOHaD Society (www.mrc-leu.soton.ac.uk/dohad/index.asp) is flourishing, with members in 57 countries, a widely read journal (www.journals.cambridge.org/doh) and representation on several international bodies. There is widespread recognition that early life processes affect the later risk of a range of diseases, especially NCDs, and the developmental aspect of a lifecourse approach to health is now discussed at a policy level. To date, most of the evidence for DOHaD concerns early life nutrition and exposure to stress, factors which have both direct and indirect effects on development of a range of aspects of offspring phenotype, partly via affecting maternal and placental physiology. It is increasingly recognised that these effects operate within the normal range of the developmental environment; that they induce a phenotype which may confer greater risk of later NCD through inadequate responses to challenges such as an obesogenic environment; but that they do not necessarily induce pathological changes in the offspring's development and so should not be termed disruptive or teratological. Many of these developmental processes operate via epigenetic processes which underlie the control of normal development.

As discussed extensively at PPTOX meetings, the field of toxicology has moved from focussing on teratology to the demonstration that a range of environmental factors have effects on development within the normal range. They include infectious agents, toxins, forms of radiation, pollutants, heat and chemicals, especially endocrine disruptors. Again, these can act in a non-disruptive way to influence aspects of normal development and can affect later risk of disease. The interaction between pollutants such as lead or arsenic and micronutrient supply via both the mother and the placenta is well known. But since environmental agents such as endocrine disruptors have been shown to act on epigenetic processes, even at low levels which may not in themselves be expected to be teratological, they may interact with epigenetic control linked to nutrition and endocrine function to alter the developing phenotype. Thus they may contribute to risk of NCDs. These issues are of particular concern in low income and transitioning societies.

The public health implications of DOHaD now require linking to wider environmental issues of great relevance to sustainable development globally, including pollution, climate change, urbanisation, agriculture, industrialisation and communicable disease control. This will give added value, by synergising the policy initiatives and complex interventions necessary to address these challenges to global health.

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Creating a DoHAD global network: Using other networks as a model

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Environmental exposures pose a serious health risk to millions of children worldwide, especially to those living in low- and middle-income countries. It is now well established that non-communicable diseases in adulthood are influenced not only by genetic and adult lifestyle factors but also by environmental factors acting in early life. This concept, which has been termed the Developmental Origins of Health and Disease (DOHaD) hypothesis, promotes the understanding of the link between environmental exposures and disease risk across the lifespan. To understand complex developmental exposures to a wide variety of environmental chemicals, forming an international DOHaD collaborating network would improve coordination of research priorities and raise awareness of the issues related to early-life exposures to chemicals.

This talk will outline a few of the many existing models that DOHaD researchers can take advantage of to facilitate creation of a global collaborative network. Examples of such existing networks include the Children's Environmental Health WHO Collaborating Centre (CEH WHO CC) Network; the Pacific Basin Consortium for Environment and Health (PBC) and the Central and Eastern European Environmental Health Conference (CEEHC), facilitated by the NIEHS Superfund Research Program (SRP); and other formal networks of environmental health scientists and public health investigators on issues related to disease, vulnerable populations, and/or exposures. The CEH WHO CC Network is a network of research institutions around the world with the overall goal to reduce morbidity and mortality of children. This network aims to provide a coordinated approach to addressing priority areas of children's environmental health, including early recognition of new and emerging threats to children's health such as exposure to environmental toxicants from improper electronic waste management, low-dose exposures in early life, exposure to emerging chemicals, and the effects of global environmental change. The NIEHS SRP funds university-based multidisciplinary research on human health and environmental issues related to hazardous substances. These networks foster international collaboration to communicate findings to relevant stakeholders.

Existing models can provide insight into the steps required to build an international network and highlight the advantages of creating a coordinating program that facilitates multidisciplinary and multidirectional interactions among groups worldwide. A global network would bring together scientists from multiple disciplines and countries to work toward a better understanding of DOHaD. The network will also contribute to alerting the global health community of activities among centers, raise awareness of DOHaD, and assist in targeted messaging to improve public health.

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Integration of DOHaD concepts in WHO global health efforts

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Comments on developing a DOHaD network and panel discussion

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The recent publication of 2010 global burden of disease estimates highlight the growing burden imposed by chronic non-communicable diseases. Major risk factors and their contributions to disease burden have also been published. These estimates have been made using rigid methodology that requires a sufficient level of evidence for a risk factor to be included. This approach creates a structural bias against newly recognized or emerging risk factors. The intention to update these estimates annually may cause a greater problem if additional risk factors are not included. Adverse environmental exposures in early life are among the risk factors systematically excluded from the current burden of disease estimates. Yet understanding is increasing that many non-communicable diseases have their origin in early life.

In a deliberate attempt to increase awareness of and to provide scientific evidence supporting the contribution of early life environmental exposures to chronic disease, the World Health Organization has been expanding the number of collaborating centres that have been designated in areas relevant to children's environmental health (CEH). These centres are now forming into a network to ensure effective collaboration and coordination of research efforts. To date CEH collaborating centres have been designated in Australia, Mexico, South Korea, Thailand, the USA and Uruguay. Proposed collaborating centres in Brazil, Denmark and Japan are currently in the application process. The CEH network is formally coordinated by the collaborating centre at the National Institute of Environmental Health Sciences, USA and a website is under construction. The network will encourage participation from groups and organizations that may not be able to or may not wish to become WHO collaborating centres. Groups that have either joined the network or expressed interest in doing so include: the Collegium Ramazzini, the Pacific Basin Consortium for Environment and Health and the International Society for Children's Health and the Environment.

A clear research needs that could be addressed by the network include: improving assessment of early life exposures; developing short-term outcomes and biomarkers that predict long-term risk of chronic non-communicable diseases; and linking these into the global DOHaD agenda.

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